

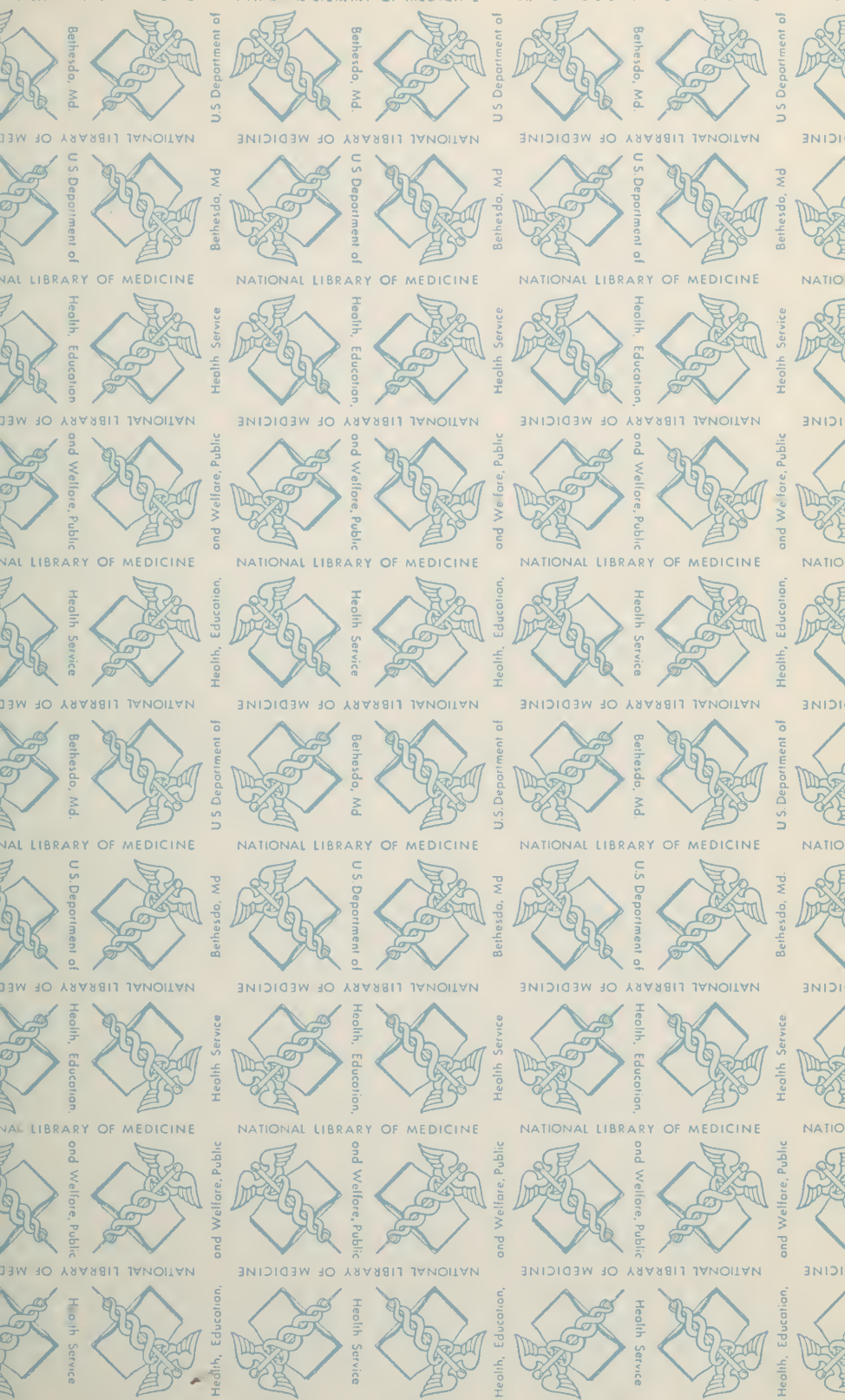
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CEREBROSPINAL FLUID

IN HEALTH AND IN DISEASE

BY
ABRAHAM LEVINSON, B.S., M.D.

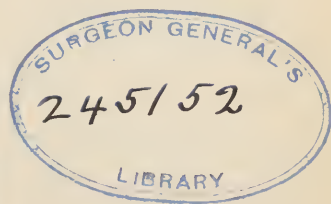
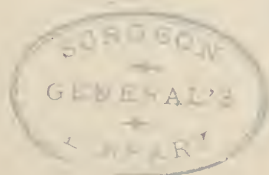
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WITH A FOREWORD BY
LUDVIG HEKTOEN, M.D.

WITH SIXTY-NINE ILLUSTRATIONS, INCLUDING
FIVE COLOR PLATES

SECOND EDITION, THOROUGHLY REVISED

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W0 V

TO HIM TO WHOM THE PRACTICE OF MEDICINE
CONSTITUTES AN IDEAL RATHER
THAN A PROFESSION,

TO HIM WHO COMBINES CLINICAL INSIGHT
AND SCIENTIFIC RESEARCH,

TO HIM WHO SEES IN MEDICINE BOTH A
SCIENCE AND A PHILOSOPHY,

THIS LITTLE VOLUME IS RESPECTFULLY
DEDICATED.

FOREWORD

By Ludvig Hektoen, M.D.

The author was kind enough to ask me if I would look over his manuscript and then tell him whether it seemed to me worthy of publication. Later, when I told him that in my opinion he had produced a valuable little book, he requested me to state the reasons for this favorable opinion in the form of a foreword. This I can do in a few brief statements.

In the first place, on reading the manuscript, I soon became aware that the author had come to his task with not only a large experience behind him in the examination by various methods of the cerebrospinal fluid as an aid in diagnosis, but with a highly creditable record in the scientific study of this fluid as well. Evidently he had been drawn to his work on the cerebrospinal fluid because of its attractiveness as a field of research, as well as on account of its importance in diagnosis.

It is to this happy combination of true philosophic interest and first-hand practical knowledge on the part of the author that the book owes its chief merit, namely, thoroughness and freshness in the parts dealing with fundamental problems, as well as in those dealing with practical matters. In the second place there could be no doubt in regard to the timeliness of a work of this kind. Indeed it seemed to me that a definite want would be supplied; for, in spite of an increasing importance in medicine, there was as yet no comprehensive book on all phases of the cerebrospinal fluid.

PREFACE TO THE SECOND EDITION

The welcome given the first edition of this book by medical reviewers as well as by the medical profession at large has encouraged me to undertake a second edition.

I have taken this opportunity to incorporate the results of the most recent research on cerebrospinal fluid. The addition of new data and the revision of old has necessitated the recasting of some chapters. Several old illustrations have been discarded and many new ones have been added. Some of the methods of examination have been simplified for practical use. References have been brought up to date, and wherever possible errors have been corrected.

A. LEVINSON.

Chicago, Ill., 1923.

PREFACE TO FIRST EDITION

Of recent years the study of body fluids has been engaging the attention of many physicians and scientists. Particularly marked has been the interest in the study of cerebrospinal fluid. Through recent investigations of this fluid, we have gained a great deal of information regarding the diagnosis and nature of many diseases and a much clearer conception of the general physiologic processes in the body. Further investigations on the subject will open up new possibilities in science and medicine, for there is hardly another body fluid that presents so favorable an opportunity for the study of physiologic and pathologic processes in the human body as the cerebrospinal fluid.

Cerebrospinal fluid is of great physiologic importance for various reasons. It is the clearest and most transparent of all the fluids of the body. It is clearer than blood, than bile, and even clearer than urine, and under normal conditions experiments may be made on it without fear of clot formation or color change. Furthermore, cerebrospinal fluid, like blood and urine, can be removed from the living body without injury to the system. This gives one the opportunity of working with processes in the living body—a distinct advantage over the study of dead tissue.

From the standpoint of pathology also, cerebrospinal fluid presents an exceptional opportunity for study. The slightest change in the color of the fluid, the smallest increase in the protein content or in the cell count, all of which are easily discernible, indicate the presence of a pathologic process. One is able to follow the course of disease throughout all stages by noting the various changes the cerebrospinal fluid undergoes from time to time. These changes may be manifested not only by the presence of the causative organisms themselves, but just as frequently by specific physical, chemical, cytologic and physicochemical processes. A close study of the changes in the cerebrospinal fluid under pathologic conditions throws light, not only on the specific diseases of the nervous system, but on the condition of other systems. One can readily see, therefore, how large is the scope for the study of cerebrospinal fluid.

In this book I shall discuss cerebrospinal fluid in its various phases, and shall attempt to show the nature of the fluid in its normal state and to point out the deviations in processes of disease. I shall incorporate the results of my own clinical and experimental studies as well as the observations of the many workers who have added to our knowledge by their researches on cerebrospinal fluid.

This little book is sent out as an humble contribution, as

I am fully aware of its many shortcomings and omissions; but if it saves the busy practitioner the irksome task of consulting countless sources for information on cerebro-spinal fluid, I shall feel that the work has not been in vain. And if perchance it should serve to stimulate even one zealous student to help solve some of the problems presented, I shall feel that my effort has been amply rewarded.

Many of the investigations that have found their way into this volume would not have been possible without the constant cooperation of certain institutions and individuals. I, therefore, take this opportunity of expressing my gratitude to them collectively and individually—to the attending staff, internes and nurses of the Michael Reese Hospital in general, and the Sarah Morris Hospital for Children in particular, to Dr. Katharine Howell, serologist of the Nelson Morris Institute for Medical Research, to Professor F. C. Becht of the Department of Pharmacology of the Northwestern University, and to Dr. G. Bartelmez of the Department of Anatomy, University of Chicago.

Particular thanks are due to Professor Ludvig Hektoen of the University of Chicago for his helpful suggestions and for his careful reading of the manuscript, and to Professor Shiro Tashiro of the Department of Biochemistry of the University of Cincinnati for his tireless assistance in checking up many of the experiments. Thanks are also due the editors and publishers of the many journals for their permission to republish some of my articles that appeared in their journals.

A. LEVINSON.

Chicago, Ill., 1919.

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CEREBROSPINAL FLUID

CHAPTER I

HISTORY OF CEREBROSPINAL FLUID

The existence of water on the brain in pathologic cases was known to the ancients. Hippocrates (460-370 B. C.) is credited with tapping the ventricles in hydrocephalus. We have nothing to show, however, that the ancients knew of the existence of fluid in normal persons. There is no mention of cerebrospinal fluid in the early writings of Hippocrates. In the later Hippocratedian collection the brain is spoken of as a gland. The glandular nature of the brain in this instance, however, does not refer to the cerebrospinal fluid, but to the so-called secretion which the ancients believed was poured down from the brain into the pharynx. Herophilus (280 B. C.) the discoverer of the torcular Herophili and of the fourth ventricle of the brain, knew of the existence of the chorioid plexus but not of its function nor of the contents of the ventricles. It seems but natural to suppose that Herophilus who dissected hundreds of human bodies should have known of the existence of cerebrospinal fluid in the ventricles. Yet, in giving a description of the ventricles which he speaks of as the seat of the soul, he makes no reference to the presence of any fluid in the brain. There is a possibility, of course, that the lost books of Herophilus may have contained some reference to cerebrospinal fluid.

One finds the same silence on the subject in other ancient authorities. Erasistratus of Julis (330-250 B. C.) describes four cavities in the brain, but he makes no mention of fluid

in them. Galen (131-201 A. D.), who was thoroughly familiar with the construction of the ventricles, speaks of an "excrementitial liquid, expressed from several places in the brain into the ventricles, especially the fourth, where this liquid is stored and then purged into the nose through the ethmoid bones and infundibulum." The fluid referred to, however, may or may not have been the cerebrospinal fluid. Hemesius of Emersa (born 340 A.D.) gives a minute analysis of the ventricles and the localization of mental power within them, but he does not speak of the fluid they contain.

One would naturally turn to Vesalius for a description of cerebrospinal fluid, for it is a well-known fact that Vesalius knew the chorioid plexus and, therefore, may also have observed the fluid. Yet, though he devotes page after page to a discussion of the localization of the soul, he merely mentions a watery humor of the brain, but gives no description of any humor that would indicate that he had the cerebrospinal fluid in mind. Mention of the presence of a fluid in the brain is found in the writings of Varolius (1543-1575). This scientist, who described the pons that bears his name, denied the existence of pneuma in the ventricles, and insisted that it was fluid and not pneuma that filled up the cavity of the ventricles. However, he gives no description of the fluid he recognized.

The real discovery of cerebrospinal fluid is attributed to Contugno. Dominico Contugno is responsible for many discoveries in medicine. He discovered intestinal lesions postmortem in a case of typhoid; demonstrated the presence of albumin in urine on boiling; and discovered the aqueduct in the internal ear known subsequently as the aqueductus Contugni. In 1784 he made the important discovery of the presence of cerebrospinal fluid in living fishes and turtles, although he could not detect its presence in man. Though Contugno usually gets the credit for the discovery of the cerebrospinal fluid, Bilanchoni claims that Valsalva prior to Contugno found "an ounce of a certain liquid in cutting the

cord membrane of a dog, a fluid resembling that seen in articulations."

The absence of a method whereby normal cerebrospinal fluid could be demonstrated in living beings was responsible for the lack of interest shown in the investigations of this fluid. Whatever interest was manifested, was confined to pathologic cases. In 1727 Stalpartius Vander Wiel described a case of injury to the head in which a clear watery fluid was seen to escape from the ear for several days after the injury. In 1764 Robert Whytt appeared with a description of tuberculous meningitis. He divided the disease into three stages according to the behavior of the pulse, and attributed the various manifestations of the disease to the presence of a serous exudate. In 1768 he published the results of his work on acute hydrocephalus under the title "Observations on Dropsy of the Brain." Under the heading of acute hydrocephalus he included all forms of acute brain disease.

A discussion of cerebrospinal fluid in normal persons is contained in the writings of Albertus de Haller (Fig. 1). In the "First Lines of Physiology" in the third Latin translation, we find the following:

"The fluids, which, being deposited from the blood into other vessels, are said to be secreted, seem reducible to four classes. The first consists of viscid fluids, coagulable by a heat of about 150° , by alcohol, and by strong acids, although generally, in the living animal, they escape in the form of vapor and after death are compacted into a gelatinous substance. To this class belong the liquor and halitus of the ventricles of the brain, the pericardium, pleura, peritoneum, tunica vaginalis, amnios, joints, renal capsules, and probably of the womb, with the juices of the stomach and intestines, and lastly the lymph generally known."

A little further Haller goes on as follows:

"Have lymphatic vessels been seen with certainty in the brain? They have been described in the large chorioidal

plexus amongst the fibers of the olfactory nerve, and in the pia mater. For my own part, I have never seen them, and it is probable that there are none, since there are no conglomerate glands in the brain, which are always found near these vessels. As for the various accounts which are given of the pituitary glands, of the infundibulum and of the ducts which lead from thence into the veins of the head, absorbing water from the ventricles, they are not supported by any anatomic demonstration; which makes it probable that the vapor, which is secreted into the ventri-



Fig. 1.--Albertus de Haller (1708-1777).

cles of a healthy person, is, in like proportion, absorbed again by the inhaling veins; and that if there be any excess, it descends through the bottom of the ventricles to the basis of the skull, and into the loose cavity of the spinal marrow. That this is the case, appears from the palsies, which ensue after apoplexies and from the watery tumors in the lower part of the spinal marrow, in hydrocephalic patients.”

It is evident from Haller's statement that he knew of the

existence of cerebrospinal fluid in the ventricles, although he spoke of it as a vapor.

Haller thought that the fluid or vapor also flowed into the small tubes of the nerves. In the quotation that follows may be found part of Haller's explanation of the mechanism of irritability, the original conception of which was advanced by Glisson.

"Upon the whole, it seems to be certain that, from the vessels of the cortex, a liquor is secreted into the hollow tubes of the medulla, which, being continued into the small tubes of the nerves, and propelled to their extremities, is the cause of both sense and motion. But there will be a twofold motion in that humor; the one slow and constant from the heart; the other, not continual, but exceedingly swift, which is excited either by sense or any cause, as motions arising in the brain."

Although Haller knew a great deal more about cerebrospinal fluid than his predecessors, it is apparent from his own statements that he was not aware of the real nature and composition of the fluid. It was left to Magendie (Fig. 2) (1825) to give us an accurate description of the workings of the fluid, especially the fluid at the base of the brain. We are indebted to him for a clear-cut description of the physical appearance and protective function of the cerebrospinal fluid. The following is taken from Magendie's treatise on *Physiology*:

"But there is a disposition unknown to Bichat, which I have recently discovered, and which contributes in a manner extremely efficacious to the conservation and defense of the medulla.

"The canal which is formed around the medulla by the pia mater, and which is lined by the arachnoid, is a great deal larger than is necessary to contain the organ; but during life the whole interval is filled up by a serous liquid, which strongly distends the membrane and which spouts out to many inches in height from a small puncture made

in the dura mater. An analogous arrangement is also to be observed around the brain and cerebellum. It is easy to conceive how efficacious must be the protection thus derived from the liquid which surrounds the spinal marrow, and in the midst of which it is suspended like the fetus in utero; with this difference that it is fixed in its position by the ligamentum dentatum, and the different spinal nerves.

“Besides the different envelopes of the brain of which we have spoken, and the dura mater which covers it in its



Fig. 2.—François Magendie (1783-1855).

whole extent, this substance is everywhere surrounded with a very fine serous membrane the principle use of which is to yield a thin fluid, which lubricates the brain. The arachnoid penetrates to all the cavities of the brain.”

It is evident, therefore, that Magendie knew not only of the existence and appearance of the cerebrospinal fluid, but that he was also aware of the most significant function of the fluid—namely, its protective nature.

As soon as Magendie opened the way for the study of

cerebrospinal fluid, a number of other investigators followed in his path. Luschka and Eckar studied the fluid from an anatomic standpoint. Cavazzani performed numerous experiments on dogs to determine the physiologic character of the cerebrospinal fluid. Naunyn made a study of the physics of cerebrospinal pressure. Shortly after, in 1842, Lange's *Anatomy* appeared and in it were nine pages devoted exclusively to a discussion of cerebrospinal fluid, —a discussion that was both lucid and graphic.

Almost simultaneously speculation began as to the source of cerebrospinal fluid. Carl Schmidt, in 1850, expressed the view that the cerebrospinal fluid was not a mere transudate from the blood. Faivre, in 1853, advanced the theory that the fluid was a secretion. Numerous investigations followed the promulgation of this idea, and hundreds of experiments were undertaken by anatomists, pathologists, physiologists, and chemists, experiments that are being carried on to this very day.

With the discovery of a method whereby cerebrospinal fluid could be removed from the living body, a new era was ushered into the history of this fluid. One of the first means of obtaining the cerebrospinal fluid was by removing it from the skull. This operation was fraught with many difficulties. It involved the use of a great number of instruments and necessitated trephining of the skull and the making of a scalp wound.

A great improvement was made on this method in 1885. Corning injected 20 minims of a 2 per cent solution of hypochlorate of cocaine into a space situated between the spinous processes of two of the inferior dorsal vertebræ of a dog. Five minutes after the injection there were marked evidences of incoordination in the posterior extremities. A few minutes later there was pronounced weakness in the hind legs, but there were no signs of feebleness in the anterior extremities. The faradic current

showed that there was no reflex action of the hind legs, but the anterior extremities responded quickly.

Corning then injected 30 minims of a 3 per cent solution of cocaine hypochlorate between the spinous processes of the eleventh and twelfth dorsal vertebræ, in a man suffering from spinal weakness. As there was no numbness noticeable, he injected 30 minims more in the same spot about six or eight minutes later. In ten minutes the man complained that his legs felt "sleepy," and brush applications showed that sensibility was greatly impaired.

As a result of his experiments Corning came to the conclusion that local medication by means of spinal puncture could prove of great therapeutic value in relieving a number of morbid conditions of the cord. Unfortunately, however, Corning left us neither a description of the technic he employed nor of the type of needle he used. Moreover, his operation was attended with a great degree of risk in that he introduced the needle too high up in the spinal column, thus incurring the danger of injury to the cord.

In 1891 W. Essex Wynter reported the drainage of cerebrospinal fluid in four cases of tuberculous meningitis. He treated his first case in 1889, making an incision in the skin of a patient suffering from tuberculous meningitis. In the incision which was made a little to one side of the spine of the second lumbar vertebra, he introduced a Southey tube and a trocar. When he felt that the point of the trocar had struck against the lamina, he directed it slightly downward, forced it through the ligamentum and theca, and then inclined it toward the median line. When the trocar was withdrawn, clear fluid rushed out into the Southey tube. A fine, India-rubber tube was then connected to facilitate continuous drainage. The symptoms of the disease subsided immediately, although the patient subsequently died from tuberculous meningitis. From 1889 to 1891, Wynter treated three more cases of tuberculous meningitis in the

same fashion, all of them showing improvement for a while, although they subsequently succumbed to the disease.

Charles A. Morton (1891) followed the method outlined by Wynter. In discussing the pathology of tuberculous meningitis with reference to its treatment by tapping the spinal subarachnoid space, Morton says:

“What symptoms can be relieved by it only the practice of the operation can show; that out of four cases operated on in the Middlesex Hospital in one there should have been contraction of the unduly dilated pupils, and in another slight improvement in the general condition, is encouraging when we remember that drainage was not maintained in all the cases. The operation does no harm and as the patient is already comatose, no anesthetic is required.”

Morton, we see, tapped the patient when he was already in a comatose condition. Although he does not state definitely just what technic he employed, he does, at the beginning of his article speak of the recent procedure “of tapping the subarachnoid space of the spinal cord in cases of tuberculous meningitis.” This would seem to indicate that he followed the method of Wynter; namely incision of the skin, introduction of a trocar between the vertebrae and the use of a continuous drain.

For the simplification and perfection of spinal puncture we must turn to Quinke. Corning, who was the first to use spinal puncture, employed an operation that was fraught with danger to the cord, as the point at which he introduced the needle was too high up in the spinal canal. Wynter, it is true, did his puncture in the lumbar region, but his method necessitated the use of a large trocar, a continuous drain and a large incision in the skin. The procedure of Quinke was a vast improvement over those of his predecessors, both from the standpoint of simplicity and of safety. Quinke used only a plain needle and he so perfected the technic of spinal puncture that there is little that can be improved on his original method.

At the Tenth Congress for Internal Medicine, Quinke reported two cases of hydrocephalus treated by means of withdrawal of the cerebrospinal fluid. The first was one of chronic hydrocephalus in which the fluid was removed by trephining and in which the contractures of the extremities and of the neck subsequently disappeared. The second was that of a child in which lumbar puncture resulted in great improvement. From these and similar observa-

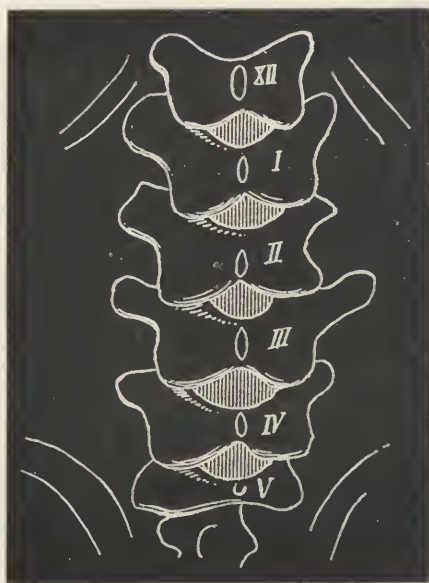


Fig. 3.—Drawing accompanying original article on lumbar puncture by Quinke, representing lumbar region of skeleton of a one-year-old child.

tions Quinke concluded that spinal puncture for therapeutic purposes was indicated in marked cerebral pressure, especially in cases of tuberculous meningitis and acute hydrocephalus. Quinke not only described the technic of spinal puncture, but he also measured the pressure of the cerebrospinal fluid and determined its chemical composition so far as he was able with the chemical technic at his command. (Figs. 3 and 4.)

For two years after Quinke's experiments with spinal

puncture no reports appeared in literature regarding its use. It was not until 1893 that Lichtheim called attention to spinal puncture as a valuable aid in diagnosis, and two years later, in 1895, Föbringer reported 107 punctures in eighty cases. In America, Browning, in 1894, reported a series of spinal punctures and G. W. Jacoby, in 1895-6, re-

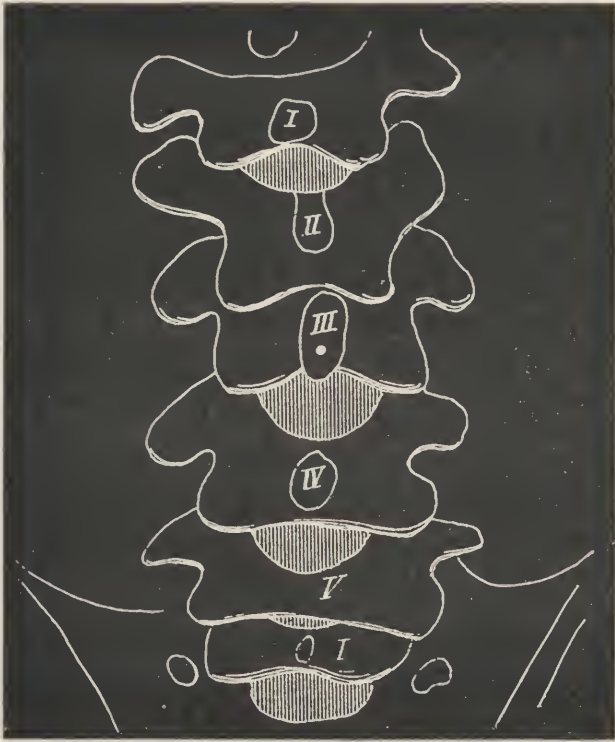


Fig. 4.—Drawing accompanying original article on lumbar puncture by Quincke, representing lumbar region of skeleton of a six-year-old child.

ported 30 punctures. Since 1896 spinal puncture has been quite generally adopted as a routine procedure for diagnostic and therapeutic purposes.

Bacteriology, serology, and chemistry have all played an important rôle in shaping the history of cerebrospinal fluid. As for bacteriology, there is hardly a discovery that does

not bear a more or less direct relation to the history of cerebrospinal fluid. The discovery of the tubercle bacillus by Robert Koch (1882) changed the name of acute hydrocephalus to tuberculous meningitis, and the conception as to its nature accordingly. The discovery of the pneumococcus by Sternberg (1881) described more accurately by Fränkel (1885), the discovery of the influenza bacillus by Pfeiffer (1892) and the demonstration of trypanosome in cerebrospinal fluid by Castellani (1903) helped to establish the cause of many inflammatory processes of the meninges.

A special chapter was contributed to the history of cerebrospinal fluid by the discovery of the meningococcus. In 1885 Leichtenstern reported four cases of epidemic meningitis and demonstrated in the pial exudate of two of the cases that came to autopsy a "few round cocci of equal size, some appearing singly, others in small irregular groups similar to the arrangement of gonococci, usually intracellular but also extracellular." In a second communication Leichtenstern reported the cultural characteristics of the bacteria found postmortem in the meningeal exudate. They were not, however, uniform. Some were short bacilli, others were long bacilli, and still others corresponded to what we now call meningococci.

Two years later (1887) Weichselbaum gave a full description of diplococci found in the direct smear of meningeal exudate observed postmortem in people who succumbed to meningitis (Fig. 5). His description of the cultural characteristics of these bacteria was so accurate that for many years very little had been added to our knowledge of meningococci. It is only in the last few years that additional knowledge has been obtained in connection with meningococci.

Serology has added a great deal to the diagnostic and therapeutic uses of the cerebrospinal fluid. Bordet's discovery of complement fixation, Ehrlich's work on immunity and Wassermann's serologic test all found practical

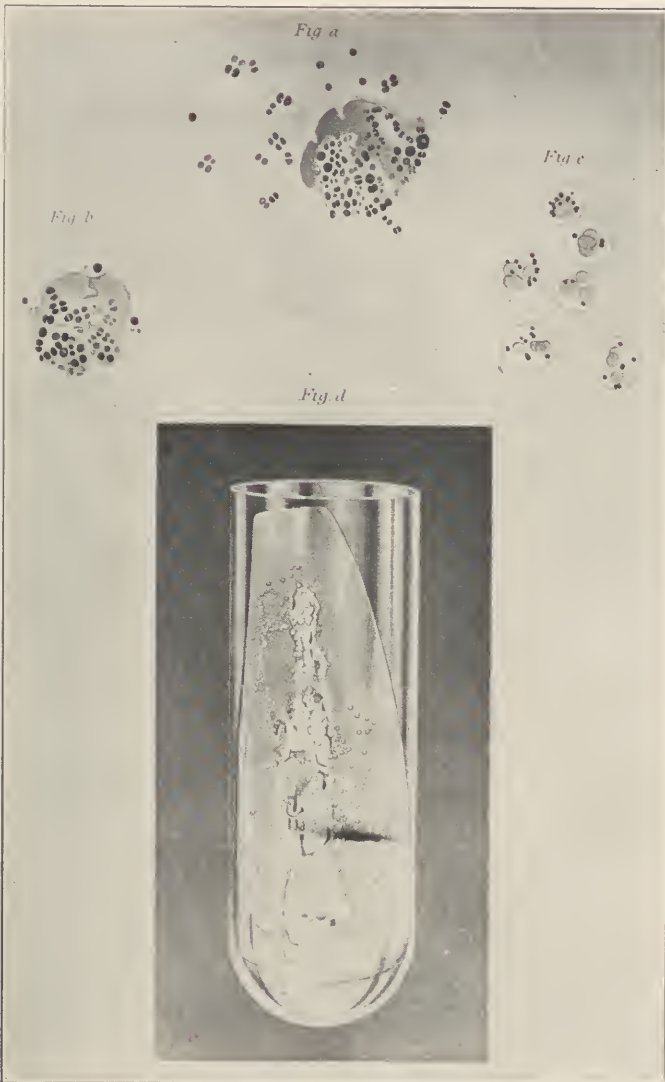


Fig. 5.—Illustration of meningococci in smear and in culture, accompanying original article of Weichselbaum in 1887.

applications in the cerebrospinal fluid. However, probably the most beneficial contribution in the field of serology was the discovery of antimeningococcus serum by Jochmann in Germany and by Flexner in America and the in-

roduction of the intraspinal injection of the serum by Flexner.

Chemistry, too, has had its share in shaping the history of the cerebrospinal fluid. Lassaigue determined the composition of cerebrospinal fluid for Magendie. Halliburton worked on the chemical composition of fluid from cases of rhinorrhea obtained by Sir St. Clair Thomson. Many other chemists and physiologists also worked on the nature of the cerebrospinal fluid.

Chemistry has not only taught us the composition of this, the clearest of body fluids, but has also shed light on the diagnosis of meningitis and other affections of the central nervous system.

Cytology advanced the study of cerebrospinal fluid to a great degree. Widal, Ravaut, and Sicard led the way in this phase of study, and they were followed by many workers on the subject.

Finally, the recent offspring of science, physical chemistry, is making its impress also on the history of cerebrospinal fluid. The H-ion concentration, cataphoresis, the Lange colloidal gold test, the ninhydrin reaction and the precipitation tests, all of which are based on physicochemical principles, have thrown light on diseases of the central nervous system in general and on the composition of body fluids in particular.

We see that it would hardly be an exaggeration to say that the history of cerebrospinal fluid in many respects is but a miniature history of modern medicine.

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CHAPTER II

ANATOMY AND PHYSIOLOGY OF CEREBRO- SPINAL FLUID

The cerebrospinal fluid (*liquor cerebrospinalis*, *liquide cephalorachidien*, *Zerebrospinalflüssigkeit*) is contained in the ventricles of the brain and in the subarachnoid space of the brain and cord.

THE VENTRICLES

The ventricles of the brain are five in number, two lateral, third, fourth and fifth (Figs. 6 and 7).

Each one of the two lateral ventricles is located in the central part of the cerebral hemisphere and is divided into a central portion, an anterior or ascending, a posterior and an inferior or descending horn.

The central portion or the body of each ventricle lies in the region of the parietal lobe. The anterior horn passes from the body forward and outward into the frontal lobe. The posterior horn passes backward and outward into the occipital lobe. The inferior horn passes downward and outward into the temporal lobe. The two lateral ventricles are separated from each other by a thin triangular partition called the septum pellucidum. This partition forms the inner wall of the body of each ventricle. It also encloses the fifth ventricle.

The third ventricle is a narrow triangular cleft extending from the aqueduct of Sylvius or the cerebral aqueduct to the lamina terminalis. It measures about an inch in length from before backwards and a quarter of an inch in breadth at its widest part. It opens in front through the foramina of Monro (interventricular foramina) into the

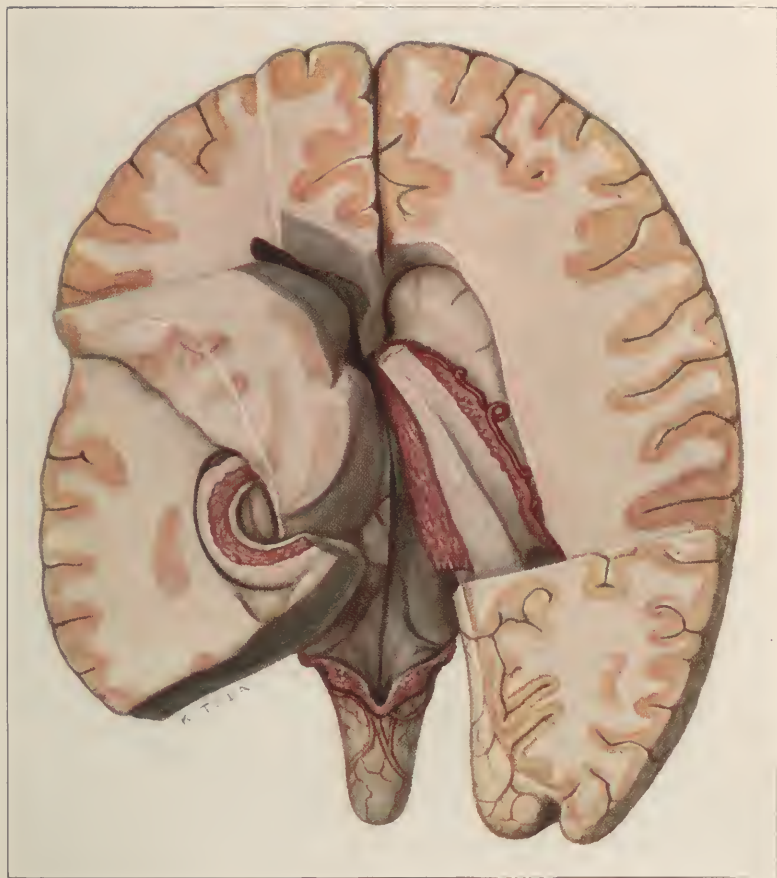


Fig. 6.—Section of human brain showing the chorioid plexus, the extent, relations, and intercommunications of the brain ventricles. (See Fig. 7.)

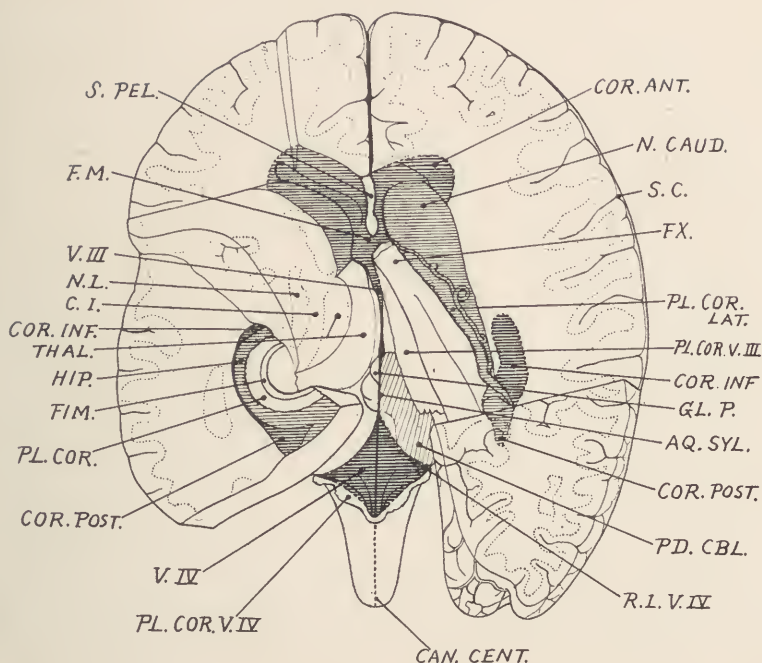


Fig. 7.—A diagram of Fig. 6. The ventricles are deeply shaded. The outlines of the ventricles which appear in Fig. 6 are indicated by continuous lines. On the right side the position of the underlying ventricular cavities is also indicated by shading, but the outline is a broken line.

S. PEL., Septum pellucidum.

F. M., Foramen of Monro.

V. III., Third ventricle.

N. L., Lentiform nucleus.

C. I., Internal capsule.

COR. INF., Inferior horn of lateral ventricle.

THAL., Optic thalamus.

HIP., Hippocampus.

FIM., Fimbria.

PL. COR., Lateral chorioid plexus.

COR. POST., Posterior horn of lateral ventricle.

V. IV., Fourth ventricle.

PL. COR. V. IV., Reflected chorioid plexus of fourth ventricle.

CAN. CENT., Position of central canal.

COR. ANT., Position of anterior horn of lateral ventricle.

N. CAUD., Caudate nucleus.

S. C., Fissure of Rolando (central sulcus).

FX., Fornix cut through at column of the fornix.

PL. COR., LAT., Lateral chorioid plexus.

PL. COR. V. III., Reflected chorioid plexus of third ventricle and septum interpositum.

COR. INF., Position of the inferior horn of lateral ventricle.

GL. P., Left half of pineal body.

AQ. SYL., Aqueduct of Sylvius.

COR. POST., Position of posterior horn of lateral ventricle.

PD. CBL., Cut surface of cerebellar peduncles.

R. L. V. IV., Lateral recess of fourth ventricle.

lateral ventricles and is continuous behind with the upper end of the aqueduct of Sylvius connecting with the fourth ventricle.

The fourth ventricle, or the cavity of the hind brain, is a diamond-shaped space, continuous at its upper end with the aqueduct of Sylvius, and at its lower end with the central canal of the spinal cord. The upper part of the ventricle is located between the pons in front and the cerebellum behind. The lower part lies in the interior of the medulla.

The fifth ventricle is a cavity in the septum pellucidum, and is entirely separate from the other ventricles. It is bounded above and in front by the corpus callosum and below and behind by the body and anterior pillars of the fornix.

A layer of cubical epithelial cells, known as the ependyma, is lining the third, fourth and fifth ventricles (Fig. 8). Whether the ependyma plays any rôle in the production of cerebrospinal fluid is a matter of conjecture.

THE CHORIOID PLEXUS

Lining the ventricles there is a tuft of blood vessels, covered by a single layer of epithelium called the chorioid plexus, commonly spoken of as the choroid plexus (Figs. 6, 7, and 8). This plexus is an ingrowth or folding of the pia, the layer of the meninges immediately adjacent to the brain.

Two-thirds of the blood supply of the plexus in man is furnished by the anterior chorioid branch of the internal carotid artery which enters the plexus at the anterior end of the descending horn of the lateral ventricle. The remainder is supplied by the posterolateral chorioid artery, a branch of the posterior cerebral. These arteries break up into arterioles, the largest of which are visible to the naked eye. After passing through the network of capilla-

ries, the blood returns through the chorioid vein to the internal cerebral veins where it joins its fellow and forms the cerebral vein, or vein of Galen.

The walls of the blood vessels of the chorioid plexus, measure, in some tufts, 0.2 mm. in thickness, while in others they form only a thin membrane between the lumen and the cuboidal cells on the surface. Much variation exists also in the size of the lumina.

Sundwall divides the vessels of the chorioid plexus into two groups: (1) The vessels with thick walls, which as a rule, possess narrow lumina and have the same general structure as the small arteries. Weigert's stain shows a well-developed internal elastic layer, which in most instances is corrugated. In the media, which is quite well developed, fine, wavy, elastic fibers may be seen. The fibers may be traced to the cuboidal cells for which they frequently form a basic membrane. (2) The second group of vessels are those with comparatively thin walls and wide lumina. These may be regarded as veins or sinuses. No muscular tissue can be made out in the walls of this second group, the walls being composed almost entirely of white fibrous connective tissue and are so similar throughout in their structure that they can not be differentiated into intima, media, and adventitia. Only here and there may be seen a few fine elastic fibers.

The walls contain numerous small vessels and capillaries (vasa vasorum) of varying caliber. They are rich also in nuclear elements, such as endothelial cells, connective-tissue cells and interstitial granule cells.

COMMUNICATIONS

The cerebrospinal fluid in one ventricle of the brain communicates directly with the fluid in the other ventricles through the various openings connecting them. The only exception to this rule is the fifth ventricle which contains

very little or no fluid. Thus, the fluid in the lateral ventricles flows into the third through the foramina of Monro, and the fluid in the third communicates with that in the fourth by means of the aqueduct of Sylvius. (Figs. 6 and 7.)

The cerebrospinal fluid of the subarachnoid space com-



Fig. 8.—Photomicrograph of chorioid plexus. $\times 140$. The blood vessels are engorged. At the lower portion of the field the ependymal lining of the ventricle is shown.

municates with the fluid in the ventricles of the brain through the foramen of Magendie which opens into the posterior part of the fourth ventricle and through the foramina of Luschka and numerous other apertures which open into the lateral ventricles. Some authors, notably Schmorl, claim that no communication exists between the cerebrospinal fluid in the ventricles of the brain and the

fluid in the subarachnoid spaces of the brain and cord. They base this claim on two observations: (1) the finding of bile in cases of icterus in the cerebrospinal fluid of the cord, but not in the fluid of the ventricles; (2) on Schmorl's finding of a positive Nonne-Apelt reaction in the cerebrospinal fluid of the cord and a negative reaction in the fluid of the ventricles.

The best evidence that a communication exists between the ventricles of the brain and the subarachnoid spaces is the commonly observed fact that in hemorrhage into the ventricles the fluid obtained by lumbar puncture contains coagulated blood. It is also well known that when a colored fluid is injected into the ventricles, it can be recovered by lumbar puncture in a few minutes. Vice versa, if the colored fluid is injected between the atlas and axis it can be recovered from the lateral ventricle. It is also well known that a tense fontanelle will go down with the withdrawal of cerebrospinal fluid by lumbar puncture. All this points to a direct communication between the ventricles of the brain and the subarachnoid space.

THE MENINGES

The meninges of the brain and cord consist of three layers: the dura mater, the arachnoid and the pia. These three layers are separated from each other by two spaces—the subarachnoid and the subdural.

The dura mater, or the outer layer of the meninges, is rough externally and smooth and shiny internally. It consists of a cranial and a cerebral portion. The cranial portion serves as internal periosteum for the cranial bones.

The inner layer of the dura mater is covered by the parietal layer of the arachnoid which in turn forms the outer boundary of the subdural space.

As the cranial nerves enter the foramina in their exit from the cranium, they receive a tubular prolongation of

the dura, which accompanies the nerve trunk for a short distance. This prolongation, called the dural sheath, is separated from the nerve by the underlying subdural cleft, and finally becomes continuous with the epineurium, while the subdural space communicates with the lymph clefts within the connective tissue envelopes of the nerves.

The arachnoid or middle layer of the meninges is a delicate connective tissue structure located between the dura externally and the pia internally. Over the summit of the cerebral convolutions, the arachnoid and pia are so closely united that they constitute practically a single membrane.

In other places, however, these layers are connected only by the trabecula of arachnoid tissue.

The subarachnoid space is situated between the inner vascular layer of the meninges, the pia and the middle layer of the meninges, the arachnoid. The space is subdivided into numerous compartments by means of delicate trabeculae, which run from the pia to the arachnoid. In some places the subarachnoid space is quite wide and the trabeculae are quite long; whereas in others, especially over high convolutions of the brain, the opposite is the case, the space being very small and the trabeculae very short. The various wide spaces are known by special terms suggestive of their form. Among the most important are the cisterna magna, or cisterna cerebellomedullaris which is located between the medulla and the under surface of the cerebellum; the cisterna pontis which is located on the ventral aspect of the pons and the cisterna basalis or cisterna interpeduncularis, which stretches from the upper ventral border of the pons to the orbital surface of the frontal lobes.

The pia mater covers the brain closely, dipping into the fissures and sulci and covering the convolutions.

It consists of five layers of tissue, an external and an internal layer of endothelium, which cover an external and

internal elastic layer, the latter of which encloses a middle layer of connective tissue which contains pigment cells.

The cranial pia mater forms two triangular folds, the tela chorioidea superior and the tela chorioidea inferior.

RATE OF FORMATION

The rate of formation of cerebrospinal fluid is still a matter of conjecture. Falkenheim and Naunyn observed that from 1 c.c. in six minutes to 1 c.c. in forty minutes flowed out of a cannula introduced into the subarachnoid space of a dog. In another dog, weighing 23 kilos, they observed as large a flow as 240 c.c. of fluid in twenty-four hours and in still another dog, weighing 20 kilos, they reported a flow of 36 c.c. in twenty-four hours. According to these experiments there does not seem to be any relation between body weight and the rate of formation of cerebrospinal fluid nor between the rate of formation and the arterial pressure. In the numerous reports of cases of cerebrospinal rhinorrhea, the amount of fluid flowing out from the nose varied from 96 c.c. to 720 c.c. per day. Tillaux, for instance, reports a case in which there was communication between the subarachnoid space and the dura and in which the daily flow of cerebrospinal fluid from the nose averaged one-fourth of a liter. Wallace MacKenzie reports a case of cerebrospinal rhinorrhea where the average flow of fluid per hour was one ounce, making a total of 720 c.c. in a day. In trauma of the spinal column even greater amounts of fluid have been observed, as in the case of Giss in which there was a flow of fluid measuring from one and one-half to two liters. It seems likely, however, that the large amounts of cerebrospinal fluid observed in cases of trauma are no indication of the normal rate of formation of cerebrospinal fluid, as it is well known that whenever there is irritation of a serous membrane there is an increase of the fluid in the cavity.

So far as we know, no one has as yet determined the rate

of formation of cerebrospinal fluid under normal conditions.

That the cerebrospinal fluid has a circulation has been shown by Magendie, but the mode of circulation has not been entirely established. Kramer, in 1912, showed that when methylene blue is injected into the lumbar portion of the subarachnoid cavity of a dog and the animal is killed ten to twenty minutes later, the stain is found over a varying distance of the surface of the spinal cord, at times all the way to the medulla, at other times not so far. The floor of the fourth ventricle, however, is stained with methylene blue as are the cerebellum, the aqueduct, the entire ventricular system of the brain, the subarachnoid space at the base of the brain, as well as the sheaths of the cranial nerves. Blackfan and Dandy injected phenolsulphonephthalein intraspinally and were able to demonstrate the dye a few minutes later in the ventricles of the brain. This shows that there is not only a circulation of the cerebrospinal fluid downward but also upward toward the ventricles. It is thought that the fluid starts in the ventricles of the brain, that it passes through the foramina of Magendie and Luschka into the subarachnoid space of the brain, then downward along the posterior aspect of the spinal cord. On reaching the end of the cord the fluid passes upward along the anterior surface of the cord. Some of the fluid is absorbed there. The rest spreads over the convexities of the hemispheres from whence it is absorbed.

RATE OF ABSORPTION

The data on the rate of absorption of the cerebrospinal fluid are not numerous. Duret was able to introduce 583 c.c. of water into the subarachnoid of a dog in the course of two hours. Naunyn and Schreiber introduced 400 c.c. of physiologic salt solution into the subarachnoid space of

a dog, weighing $9\frac{1}{2}$ kilograms, in the course of an hour and three quarters, using 100 mm. mercury pressure for the injection. Falkenheim and Naunyn showed that the absorption is rapid even when the fluid is injected with very little force. Dandy and Blackfan injected 1 c.c. of phenol-sulphonephthalein into a dog after withdrawing 1 c.c. of cerebrospinal fluid. They examined the quantity of phenol-sulphonephthalein excreted in the urine by a colorimetric method, and found that in the first hour after the injection there were 16.6 per cent of phenolsulphonephthalein excreted in the urine; in the second, 17.8 per cent; in the third, 13.6; in the fourth, 7.2 per cent; in the fifth, 4.5 per cent; in the sixth, 2.2 per cent; in the seventh, 1.3 per cent; and in the eighth, 1.3 per cent. From these experiments they concluded that the absorption of the cerebrospinal fluid is fairly regular for a period of from three to four hours, and that it diminishes progressively after this time. They set a minimum of four to six hours for the completion of absorption of the fluid, making four to six renewals in 24 hours.

The above, however, can not be taken as an index for the rate of absorption of the cerebrospinal fluid, as phenol-sulphonephthalein is a foreign substance, and, as is well known, a foreign substance is rapidly eliminated from the body, without reference to the absorption power of the body fluids. One, for instance, is not justified in saying that since 60 per cent of a dye is excreted in the urine in two hours by the kidney, 60 per cent of the water of the blood is excreted in two hours. Foreign substances are eliminated by a special mechanism and bear no relation to the absorption of the body fluids.

So far the rate of absorption of cerebrospinal fluid has not been determined, and I believe will not be determined so long as the rate of formation of the fluid is not known, for the rate of absorption naturally depends on the rate of formation.

CHANNELS OF ABSORPTION

Quinke was able to trace cinnabar, injected into the subarachnoid space, along the sheaths of the upper spinal nerves, along the sheaths of the optic nerves as far as the episcleral space of Schwalbe, and in the Pacchionian granulations. He could find no cinnabar granulations in the visceral organs or in the general circulation. Mott considers the perivascular lymphatics as the channel of absorption. It has been proved by others, also, that a portion of the fluid is drained by the lymphatics into the deep cervical glands, and that a small portion flows into the lymph vessels of the nose, the perilymph spaces of the labyrinth of the ear and in the perineural sheaths. This is somewhat substantiated by the cases of cerebrospinal rhinorrhea reported in the literature. It has been found, however, that normally the absorption by way of the lymphatic system removes only a very small quantity of the fluid. Hill, Ziegler, and Spina showed that methylene blue injected into the subarachnoid space can be recovered from the stomach in twenty minutes, while it takes hours before the lymphatics of the neck are discolored by the stain. Dandy and Blackfan introduced a cannula into the thoracic duct after they had injected phenol-sulphonephthalein into the subarachnoid space and found that there was very little absorption by the lymph, compared with that by the blood.

These and many other experiments indicate that the greatest amount of cerebrospinal fluid is absorbed into the blood stream proper. According to Schwalbe, Key and Retzius and Weed, the Pacchionian bodies or the arachnoid hypertrophied villi perform the function of absorbing the fluid. The Pacchionian bodies, however, are absent in infancy and in lower animals in whom cerebrospinal fluid is present nevertheless. This would indicate that the Pacchionian bodies are concerned only little in the absorption

of the fluid. Weed claims that the arachnoid villi transmit cerebrospinal fluid from the subarachnoid space into the cerebral sinuses by a process of filtration from a point of higher to a point of lower pressure.

PERMEABILITY

It is conceded by most observers that under normal conditions no foreign substances, or at least very few, pass from the blood into the cerebrospinal fluid. This resistance of the meninges to the entrance of a foreign substance is held to be due to the impermeability of the meninges, although, if we accept the view that the cerebrospinal fluid is secreted by the chorioid plexus we should speak rather of the impermeability of the chorioid plexus. Various experiments have been made to demonstrate this property of the chorioid.

Cavazzani injected potassium iodide into dogs intraperitoneally and recovered only very small amounts of it in the cerebrospinal fluid. Sicard, Lewandowsky, and Rotky repeated the experiment and could not detect potassium iodide in the cerebrospinal fluid at all. Lewandowsky found that a few centigrams of sodium ferrocyanide injected into the subarachnoid space rapidly produced toxic symptoms while four to six grams injected into the jugular vein in rabbits of the same weight produced no specific symptoms. This could not have been attributed to the solution employed, for a 10 per cent salt solution injected into the subarachnoid space produced only slight effects. Lewandowsky was also able to show the transmissibility of very small traces of strychnine in the cerebrospinal fluid of lower animals, but none in man. Von Jaksch and Sicard could not detect the presence of mercuric salts after incision into the skin. Livon and Bernard could detect salicylates, but in very small amounts, in the cerebrospinal fluid of a dog after intravenous injection.

Mestrezat found that when sodium nitrate is adminis-

tered to a normal individual before a spinal puncture is made, the fluid shows very little or no nitrate, while in cases of meningitis, the drug is present in large quantities in the cerebrospinal fluid.

There are a few chemical substances, however, that do seem to be transmitted from the blood into the cerebrospinal fluid, namely hexamethylenamine, alcohol and chloroform. Hexamethylenamine has been shown by Crowe, Hold and Ratsky to be present in the cerebrospinal fluid of both man and animal after administration of the drug by mouth. This observation has led to the suggestion of giving hexamethylenamine in meningitis and poliomyelitis. Alcohol was shown by Schottmüller and Schumm to accumulate in the cerebrospinal fluid in even larger amounts than in the blood.

Antitoxin passes over into the cerebrospinal fluid only in traces. Behring injected hens both subcutaneously and intravenously with tetanus toxin and found that they suffered no ill effects. However, when he injected the same amount of toxin into the subdural space the hens died from typical tetanus.

Of pathologic products, acetone, acetoacetic acid, lactic acid and bile have been found to pass over into the cerebrospinal fluid quite readily in metabolic diseases, even when the meninges are not affected. The chlorides in the fluid are increased in some cases of nephritis and the sugar is increased in diabetes.

Parasites have been found to pass over into the fluid. Castellani demonstrated trypanosomes in the fluid in cases of sleeping sickness. Van Cott and Lutz, Bloch and others found trichinae in the fluid of patients suffering from trichiniasis.

Some of the experiments on the impermeability of the meninges and chorioid plexus are not entirely convincing because they deal with negative evidence. Very frequently also the technic and method have been at fault.

It is certain, however, that there is a vast difference between the transmissibility of chemical and immune substances in health and in disease and although we may not know positively whether the meninges or chorioid plexus are entirely impermeable in health, we do know that they become permeable in disease—a fact of great importance in the genesis and also in the diagnosis and treatment of the diseases of the meninges.

FUNCTION

That the cerebrospinal fluid has a mechanic function there is no doubt. The fluid forms a water bed around the cord and brain and thus prevents the jarring from external trauma. The fluid also equalizes the pressure between the brain and the cord. Magendie, many years ago, pointed out the following:

“The cerebrospinal fluid which is barely mentioned in the classical works, not only fills out the empty spaces in the skull and spinal canal, but has a greater function, namely, to exert a continual and regulated pressure on the neuron masses.”

However, a number of other functions are ascribed to cerebrospinal fluid. Mott believes that it is the function of the fluid to give up carbon dioxide and water to the blood and to take up oxygen and sugar. Cushing, and later Frazier, suggested that the fluid may be the medium of distribution of the active principle of the pituitary to the tissues of the central nervous system, which is essential to metabolism. Halliburton considers the fluid as a Locke modification of Ringer's solution. The sugar, as in Locke's solution, serves to supply the energy, the protein serves to repair the wear and tear resulting from the action of the nervous system, and the fluid as a whole acts as an ideal, physiologic salt solution bathing the neurones and maintaining their osmotic equilibrium.

According to Gaskell the neural tube is a primitive di-

gestive canal, and the cerebrospinal fluid a primitive gastric juice. Dandy calls attention to the gill-like appearance of the chorioid plexus, which in turn inclines him to believe that the chorioid plexus and the cerebrospinal fluid are concerned in respiration. Pettit and Girard hold that the fluid has an internal secretion. Kafka holds that the cerebrospinal fluid contains ferments which serve as a protection against infection. Hassin believes that the function of the cerebrospinal fluid is to remove the waste products of the brain.

Of the various theories advanced in regard to the function of the cerebrospinal fluid, that of mechanic function has an unquestionable basis. All the other theories are either open to objection of one kind or another, or lack in sufficient evidence. Mott's theory that the cerebrospinal fluid gives up CO_2 and water to the blood, and Cushing's and Frazier's suggestion that the fluid distributes pituitary substance to the central nervous system need further confirmatory evidence. The theories of Dandy and of Gaskell do not appear at all plausible. As to the theory that the fluid destroys toxin, the objection may be raised that very few toxins are able to get into the cerebrospinal canal under normal conditions, as shown in the discussion on permeability. Halliburton's theory seems plausible, but needs confirmation. Of all the theories, the only one that has a firm basis is that of mechanical function.

ORIGIN

The question of the origin of cerebrospinal fluid is one that has engaged the attention of many physiologists and chemists, and even today the problem is far from settled, although attempts have been made to solve it through the aid of histology, chemistry, physiology, and pathology.

Carl Schmidt (1850) was the first to voice the opinion that cerebrospinal fluid was a secretion and not a transudate by

virtue of the difference in the chemical composition of the blood and the fluid. Faivre (1854) also spoke of the intimate relation between the fluid and the chorioid plexus. Jolly (1871) believed that "cerebrospinal fluid is a blood derivative and it is beyond doubt partly a result of transudation from the surrounding blood vessels and partly from the lymph spaces surrounding the blood vessels in the brain."

Luschka, Schlaepfer, Yoshimura, Ernst, Kafka, Mott and Meek found the existence of vacuoles in the chorioid plexus, and all, with the exception of Meek, connected the globules with the secretion of cerebrospinal fluid. Mott examined the chorioid plexus of human beings soon after death and, on staining with methylene blue, he found the cells of the chorioid plexus to contain many vacuoles. This, he believed, proved conclusively that the chorioid cells secreted some substance. He compared the epithelial cells of the chorioid with those of the lacrymal glands.

Physiologic evidence as to the secretion of the chorioid plexus was also brought forth by many observers. Kafka found that, after an injection of pilocarpine, the epithelial globules of the chorioid plexus were multiplied. Cavazani showed that lymphagogues did not affect the cerebrospinal fluid. His observation that the alkalinity of cerebrospinal fluid was considerably less than that of the blood also led him to the conclusion that cerebrospinal fluid was a secretion. Cappelletti came to the same conclusion regarding the origin of the cerebrospinal fluid. He found that ethyl ether and pilocarpine increased the flow of the fluid, whereas atropin and hyoscyamin retarded the flow. Pettit and Girard found that the administration of pilocarpine, muscarin and ether to animals produced a marked increase in the secretion of the plexus. Dixon and Halliburton brought about an increase in the flow of the fluid by injecting chorioid extract intravenously. They claim that the chorioid plexus contains a hormone which,

when liberated into the blood, becomes the precursor and regulating medium of the secretory activity of the plexus.

Interesting contributions to the chemical phase of the problem have been made by Schmidt, Polányi, Schottmüller and Schumm. The work of Schmidt has been mentioned. Polányi concluded, from the small protein content and the high molecular concentration of fluid in cases of hydrocephalus, that the fluid is not a transudate. Schottmüller and Schumm claimed that the fluid is not subordinate to the blood, as they had found the fluid in some cases to contain alcohol in as great and greater quantities than the blood. Leopold and Bernhard subscribe to the view of Cushing that the cerebrospinal fluid is secreted by the chorioid plexus on the ground that they were unable to find uric acid in the fluid of normal individuals.

Evidence from pathologic conditions, as to the secretive powers of the chorioid plexus has been furnished by other observers. Charles and Levy report a case of hydrocephalus in which there was hypertrophy of the chorioid plexus. Dandy and Blackfan occluded the aqueduct of Sylvius by a gelatine capsule and produced thereby an internal hydrocephalus. This would tend to show that the fluid is secreted above the aqueduct and most likely by the chorioid plexus. That part of the fluid might come from the ventricles themselves the work of Francini would indicate, as he noticed secretory phenomena of the ependyma cells of the ventricles after ether injections.

On the other hand, there are observations that would tend to show that cerebrospinal fluid is not a secretion. Mestrezat, on the basis of chemical analysis of the blood plasma and the cerebrospinal fluid, concluded that the fluid is not a filtrate, a transudate, or a secretion, but a dialysate of blood plasma produced by a passage through special epithelial cells. McClendon, on physico-chemical ground, claimed that the cerebrospinal fluid is an ultrafiltrate. Lewandowsky considered cerebrospinal fluid a lymph secre-

tion. Arguments against the origin of the cerebrospinal fluid from the chorioid plexus are brought forth by Hassin on the basis of his histopathologic studies of the central nervous system. In degenerative conditions of the brain and cord, such as in subacute cord degeneration, multiple sclerosis, softening or abscess of the brain or cord, Hassin found the subarachnoid space and the chorioid plexus to contain lipid substances. In cerebral hemorrhage he found blood pigments in the subarachnoid spaces, and in so-called solitary tubercles of the spinal cord, he found the subarachnoid to contain miliary tubercles. These findings, he believes, tend to show that the cerebrospinal fluid originates in the brain or spinal cord tissue, that it flows towards the ventricles and the subarachnoid space, that it carries with it the waste products of the central nervous system, and that it is ultimately absorbed by the arachnoid villi as well as the chorioid plexus. The function of the chorioid plexus is, therefore, the absorption and not the secretion of the cerebrospinal fluid, Hassin believes.

From the various data presented, one would be inclined to believe that the chorioid plexus is located in the ventricles for some purpose, and possibly for the secretion of the cerebrospinal fluid. Yet the evidence brought forward to prove this point is not altogether convincing.

Mott's observation of the existence of vacuoles in the chorioid plexus, an observation that has been corroborated by Luschka, Findlay and Galeotti, does not necessarily indicate that the chorioid plexus secretes cerebrospinal fluid. Meek believes that the vacuoles are due to the melting of the fat in the epithelial cells of the chorioid through the action of such hardening fluids as alcohol and xylol, for chorioid cells which have not been subjected to alcohol and xylol do not show vacuoles. Pettit and Girard believe that these vacuoles are due to mechanical injury and to postmortem changes. Becht argues that secreting cells should not show vacuoles at all, but should be smaller

than ordinary cells. He points out the fact that secreting cells in the parotid and other glands become smaller during the period of activity, whereas those of the chorioid plexus become larger. He notes other differences as well. While, in most glands, during the period of activity the cytoplasm is differentiated into an inner granular layer and an outer clear zone with well-defined nuclei, in the chorioid plexus, during activity, the very opposite takes place. The cytoplasm becomes differentiated into an inner clear and an outer granular zone and the nucleus can hardly be distinguished from the nucleus of the resting cells.

Cavazzani's evidence regarding the alkalinity of the cerebrospinal fluid does not hold good, because the methods used for the determination of the reaction were not the proper ones, and with newer methods, the reaction of the fluid is found to be the same as that of the blood. As for the effect of pilocarpine in increasing the amount of cerebrospinal fluid, this does not necessarily show that the fluid is a secretion. The increase in the amount can just as readily be attributed to the action of the drug on the blood vessels.

As for the chemical evidence brought forth by Polányi, is it not plausible to assume that the cerebrospinal fluid may come from the blood, and that the smaller content of protein in the fluid be due to the changes the fluid undergoes during the process of filtration? Schottmüller's observation that there may be a greater amount of alcohol in the cerebrospinal fluid than in the blood may be explained on the ground of slower absorption from the cerebrospinal canal than from the blood, permitting the concentration to remain high in the cerebrospinal canal after most of the alcohol has made its escape from the blood through one of the organs of excretion.

Until it is possible to remove the chorioid we shall not know conclusively whether the chorioid is the seat of the

secretion of the cerebrospinal fluid. All that we can say at present with any degree of certainty is that there is proof to show that the cerebrospinal fluid is produced above the aqueduct of Sylvius.

The fact that nearly all constituents of the blood are present in the cerebrospinal fluid, and that the physico-chemical properties of the cerebrospinal fluid are practically the same as that of the blood, would make one believe that the cerebrospinal fluid is a direct product of the blood.

The data presented in this chapter may be summarized in the following points:

1. The cerebrospinal fluid is contained in the ventricles and in the subarachnoid space of the brain and cord.

2. There is a free communication between the fluid contained in the ventricular system and the fluid in the subarachnoid spaces of the brain and cord.

3. The cerebrospinal fluid has a circulation.

4. The rate of formation of normal fluid is unknown. Likewise is the rate of absorption.

5. Absorption seemingly takes place by a process of diffusion from the subarachnoid space of the brain and of the cord. Some absorption also takes place by the lymphatics draining into the deep cervical glands, into the lymph vessels of the nose, perilymph spaces of the labyrinth and into the perineural sheaths of the cranial nerves.

6. The meninges and the chorioid plexus, are not permeable, or very little so, under normal conditions.

7. The fluid exerts a mechanical function in that it equalizes the cerebrospinal pressure. The numerous other functions attributed to the fluid need further substantiation.

8. The origin of cerebrospinal fluid is unknown. There is some evidence pointing toward the theory that the chorioid plexus is the seat of origin of the fluid. There is also evidence pointing to the assumption that the fluid is a direct product of the blood or of the brain tissue.

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CHAPTER III

METHODS OF OBTAINING CEREBROSPINAL FLUID FROM THE LIVING BODY

Before the days of spinal puncture the removal of cerebrospinal fluid from the living body was effected with a great deal of difficulty. The usual method of removing cerebrospinal fluid from dogs was by means of a fistula between the occiput and the atlas. From human beings cerebrospinal fluid was obtained through an accidental flow of fluid from the nose or ears. There are about twenty such cases on record. Another way of obtaining cerebrospinal fluid from the living body, but one used only very rarely, was an open operation either on the head or on the vertebral column.

A number of methods have been used since 1891, the year Quinke described spinal puncture, for the removal of fluid from human beings. Cazamian removed fluid from the cisterns by inserting the needle below the eye, using the sphenoidal route. Cushing and Haynes drained cerebrospinal fluid by the open occipito-atlas route. Weggeforth, Ayer and Essick punctured the occipito-atlas route by a needle. Chartier punctured the eighth dorsal space, a method employed by Corning as far back as 1885.

Of all the methods described, lumbar puncture is the method of choice. As a rule it is easier to obtain fluid by the lumbar route than by any other route. Next to lumbar puncture ventricular puncture should be done, if the ventricles contain large quantities of fluid, as, for instance, in obstructive hydrocephalus. As a last resort the cistern puncture may be used.

LUMBAR PUNCTURE

Lumbar puncture is an operative procedure. It not only pierces the skin, fascia, muscle, ligament and dura mater, but it disturbs the equilibrium of the spinal canal by the withdrawal of fluid from the canal. It should therefore be done only when there is a good indication for it. How-

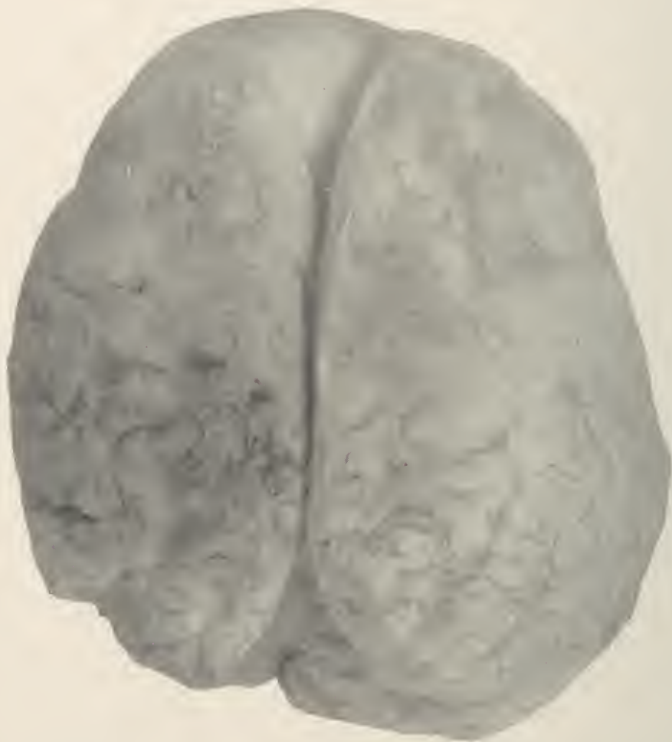


Fig. 9.—Specimen illustrating the importance of spinal puncture for diagnostic purposes. S. C. entered the hospital with symptoms of pneumonia and with marked cyanosis. At first sight there seemed to be no indication for a spinal puncture, but when convulsions set in, a puncture was done. The fluid withdrawn was very turbid and showed pneumococci in direct smear as well as in culture. The postmortem showed a well-defined exudate of the meninges, the exudate containing many pneumococci.

ever, when indicated, no fear of possible untoward effects should prevent one from doing a lumbar puncture.

The first lumbar puncture by Quinke in 1891 was done for therapeutic purposes. Since that time, however, we

have learned a great deal about the value of lumbar puncture for diagnostic as well as for therapeutic purposes. Therapeutically, lumbar puncture is done for the relief of increased intracranial pressure as in hydrocephalus, delirium tremens, eclampsia, encephalitis and other convulsive conditions. Of great value is lumbar puncture for the purpose of injecting serum in cases of meningococcus



Fig. 10.—Opposite view of Fig. 9. (See Fig. 9 for description.)

meningitis, for the intraspinal treatment of neurosyphilis, and for spinal anesthesia. Lumbar puncture is also done by some for the relief of general edema in cases of nephritis. Several cases are reported of meningeal hemorrhage which recovered after lumbar puncture. Cure by spinal puncture has also been reported in two cases of diabetes insipidus. As a general rule, therefore, a spinal punc-

ture should be made in all cases showing signs of increased intracranial pressure.

Diagnostically, lumbar puncture is of great value in cerebrospinal lues, hemorrhage of the brain, tumors of the cord, poliomyelitis, and meningitis. It is particularly valuable in the diagnosis of all forms of meningitis and poliomyelitis. The following cases are cited to show how important a diagnostic measure spinal puncture may be:

S. C. entered the hospital with symptoms of pneumonia and cyanosis. The lung findings were indefinite. There was very little rigidity of the neck and no other symptoms pointing to meningitis. At first sight there seemed to be no indication for a spinal puncture, but when convulsions set in a puncture was made. The fluid withdrawn was turbid and showed pneumococci in smear and culture. The postmortem showed the lungs to be congested, but no pneumonia. The cerebrum, however, was covered with a gelatinous, greenish gray, purulent material several millimeters thick and very firm; the exudate was located on the upper and lateral surfaces of the brain. (Figs. 9 and 10.) The smears as well as the cultures showed gram-positive cocci.

Although in this case not much could have been done therapeutically even if the process had been recognized earlier, the spinal puncture was of great value. It served to establish a positive diagnosis in a case in which a meningeal exudate existed with few if any of the meningeal symptoms that usually accompany such a condition.

The case that follows illustrates even more vividly the importance of lumbar puncture:

S. W., ten years old. Sick for five days. Complained of pain in lumbosacral region, and also in the right hip, radiating to the sole of the foot at times; occasionally there was pain in the left shoulder. When first seen the temperature was 102° F. There was tenderness to touch in the lumbosacral and gluteal regions, slight rigidity of the neck, slight Kernig and contralateral Brudzinski signs. The diagnosis by several physicians was neuritis. On lumbar puncture a very turbid fluid was obtained under great pressure. Bacteriologic examination showed meningococci and several hundred cells per cubic millimeter. All globulin tests were positive. The patient was given several doses of antimeningococcus serum and recovery followed.

In this case lumbar puncture was a life-saving measure. In the next case meningitis could hardly have been discov-

ered without lumbar puncture as the general symptoms were so indefinite.

F. R., aged eight months. Sick one day with fever and constipation. Had attack of cyanosis for a few minutes. General examination was negative. Lumbar puncture was done and to the great surprise of the physicians, the fluid was found very turbid and full of meningococci.

These cases are but few of a great number coming under my observation that illustrate the extreme importance of lumbar puncture. It is well known that many cases of convulsions are relieved by no other procedure than lumbar puncture.

The following outline summarizes the most important indications for lumbar puncture:

Indications for Lumbar Puncture

- | | | |
|----------------------|---|--|
| <i>For Diagnosis</i> | { | Suspicious meningitis
Suspicious poliomyelitis
Hemorrhage of the brain
Neurosyphilis
Coma
Convulsions |
| <i>For Treatment</i> | { | (a) Relief of intracranial pressure
Meningitis
Meningism
Poliomyelitis
Encephalitis
Hemorrhage of the brain
Delirium
Convulsions

(b) Intraspinal injections.
1. Serum treatment
Antimeningococcus
Pneumococcus serum Type I
Influenza
Poliomyelitis
Tetanus antitoxin
Horse serum

2. Chemicals
Neosalvarsan
Mercury
Optochin
Magnesium sulphate
Novocain
Adrenalin

(c) Miscellaneous
General edema
Diabetes insipidus
Uremia |

Counterindications

There are very few counterindications to lumbar puncture. In cases of tumors of the cerebrum and cerebellum, it is true that puncture is not so safe as under ordinary conditions. Even then, however, a lumbar puncture may be done with little trepidation if the pulse and reflexes of the patient are watched and if the amount and pressure of the cerebrospinal fluid are closely observed.

In erysipelas of the lumbar region spinal puncture is counterindicated, as the infection may be carried by the needle into the spinal canal. In the exanthemata, such as scarlet-fever, measles or chickenpox, spinal puncture should be done only when absolutely necessary for diagnostic or therapeutic purposes.

Untoward Effects of Lumbar Puncture

Deaths resulting from spinal puncture have been reported. These, however, usually occurred in cases of brain tumor. Of the many hundreds of punctures that have come under my observation I have seen only one case of death during puncture.

I believe that when lumbar puncture is done with the patient sitting up, death may result from the production of cerebral hernia, by release of the fluid at the base of the brain. This may, in part, at least, explain some of the deaths reported in the literature.

Of other dangers attending spinal puncture the following may be mentioned: Piercing of the aorta, injury to the nerves, and breaking of the needle.

Piercing of the aorta is a very rare occurrence, and when it does happen it is due to poor judgment on the part of the operator as to the depth to which the needle should be introduced.

Injury to the nerves is a complication that can easily be averted if the puncture is made at a low level in the lumbar region, preferably between the third and fourth vertebrae.

Breaking of the needle may result from undue force. If

the needle is broken directly beneath the skin, it is best to incise the skin and remove it. If it is broken deeper, however, which is generally the case, it is best to let it alone for a while. If no complications occur in several days, it is advisable to leave the needle inside. If severe pain or suppuration occurs, a radical operation should be done and the needle removed.

There are some less severe complications that may follow lumbar puncture. The most important of these are: headache, pain of the lower extremities, and edema of the skin, especially after repeated punctures.

The cause of headache after lumbar puncture is a matter of speculation. It is generally attributed to the removal of too great an amount of fluid at one sitting. Headache, however, sometimes follows even after the removal of a small amount of fluid. MacRobert has recently suggested that headache following lumbar puncture may be due to the nonclosure of the puncture hole in the arachnoid. The arachnoid tissue in a case of this kind, the author says, is pulled through the dural opening when the needle is withdrawn. This results in prolonged epidural leakage and in the lack of support of the medulla, a condition which gives rise to severe headache. This explanation sounds plausible although it requires corroboration before it can be accepted. When headache does occur after lumbar puncture the best method of treatment is to put the patient flat on his back for several hours. Occasionally it becomes necessary to resort to drugs for relief of the condition. Sodium and potassium bromide or salicylates may then be employed. Rarely is it necessary to use stronger remedies than these.

Pain of the extremities after lumbar puncture is usually due to injury of one of the filaments of the cauda equina. Rest in bed is usually all that is necessary to relieve this condition.

Edema of the skin in the lumbar region is an infrequent complication. I have seen it in but two cases after repeated

punctures. When it does occur in infants, the lumbar region should be given a rest and if necessary to introduce serum, it should be injected into the ventricles of the brain instead. When edema of the skin occurs in adults, warm cloths should be applied to the edematous region and serum given intravenously until the edema subsides, after which intraspinal introduction of serum may be resumed.

In general, lumbar puncture when indicated should not be feared because of complications.

Technic of Lumbar Puncture

To do a spinal puncture properly one must take into consideration a number of important factors.

1. The anatomic relations of the cord and its membranes at the lumbar region.

The cord, in the adult, ends at the first lumbar vertebra, and in the child, at the second vertebra, seldom at the third. The cord has its ending in the *conus medullaris*, the apex of which is continuous with the *filum terminalis*. Throughout its entire length the cord is surrounded by three membranes, the *dura*, the *arachnoid* and the *pia*. The accompanying drawing (Fig. 11) shows the membranes surrounding the cord and the *cauda equina* in a dog. The same relations also hold good in man.

2. The structures encountered between the skin and the cord, which are as follows from without inward:

- (a) Skin.
- (b) Subcutaneous fascia.
- (c) Fat.
- (d) Deep fascia.
- (e) Multifidus muscle.
- (f) Vertebral arches.
- (g) Ligamentum flavum.
- (h) Dura.
- (i) Arachnoid.

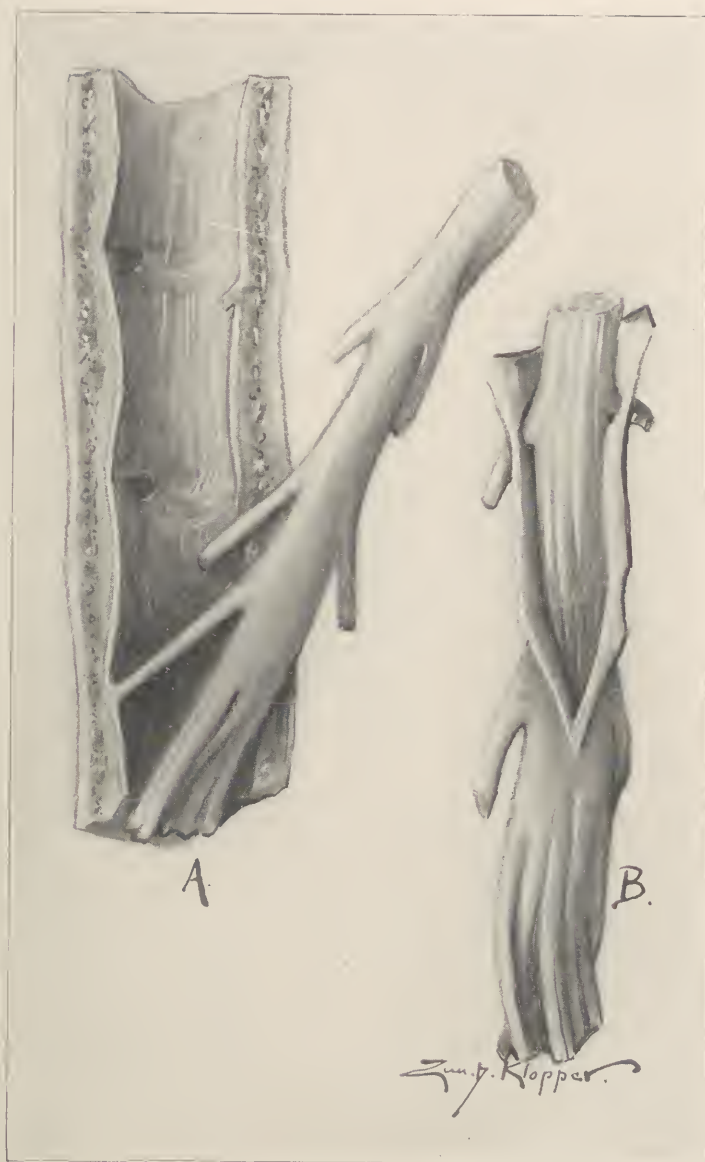


Fig. 11.—Section of cauda equina of a dog. *A*, Membranes intact; *B*, Dura and arachnoid cut open.

3. The plexus of veins on the posterior wall of the body of the vertebra (Fig. 12). If these are struck by the spinal puncture needle the resultant fluid is bloody.

Another matter for consideration in lumbar puncture is the position of the patient, particularly if the patient is a child. While in an adult the physician may do the puncture with the patient in either the sitting or reclining position, in a child he should not attempt the puncture with the patient in any but a reclining posture. In all cases of meningitis the patient should be in the lying posture when the puncture is performed. I always made



Fig. 12.—Plexus of veins, the puncture of which is responsible for blood obtained during spinal puncture. (Gray's Anatomy.)

it a practice to puncture with the patient in a recumbent position. The patient may be placed on either right or left side, the right being the preferable one for the patient, who should be arched so as to widen the intervertebral space.

The skin should be prepared very carefully for the puncture. Soap and water, alcohol and iodine should be used for cleansing purposes. Rubber gloves should be worn and all other aseptic precautions must be taken to minimize the danger of infecting the meninges. As a rule neither a general nor a local anesthetic is called for in doing a spinal puncture. It may be necessary to resort to an anesthetic

in maniacal cases, although I have not encountered a single case in which I could not get along without it. Should an anesthetic become necessary, chloroform should be the anesthetic of choice. Sophian suggests that the patient be given water to drink during lumbar puncture. He found that this procedure made an anesthetic unnecessary. As a rule, however, even this is not necessary.

The Spinal Puncture Needle

Regular spinal puncture needles are now made measuring from 7 to 9 cm. in length and 0.6 to 1.2 mm. in thickness with a stylet to fit the needle (Fig. 13). Some needles are made with valves for the measurement of the pressure of the fluid. Most needles on the market are made of steel, although there are some nickel-plated ones and some made of platinum iridium. If meningitis is not suspected a needle with a small lumen will do, but if there is the slightest suspicion of meningitis a needle with a large lumen should be used. In children it is always best to use a needle with a large lumen, so that in case the fluid is thick it will not clog the needle. The needle should be boiled and cooled before using. It should also be examined very closely for rust.

Quincke's advice that the needle be introduced directly in the midline in children and 5 to 10 mm. to one side of the midline in adults, holds good to this day. If the needle is inserted in the third or fourth interspace, cerebrospinal fluid may be withdrawn without injury to the nerves. A good landmark for the guidance of the needle may be made by drawing a horizontal line through the vertebral column across the crests of the ilium. I usually draw this line with tincture of iodine on a swab. This strikes the interspace between the third and fourth vertebra.

It is often quite difficult to feel the intervertebral space in fat people and in very young children. Because of this difficulty extreme care is necessary in cases of this kind.

“How much of the needle should be introduced into the canal?” is one of the first questions that greets the inexperienced operator. In consulting literature on the subject I found very little information about the length of the

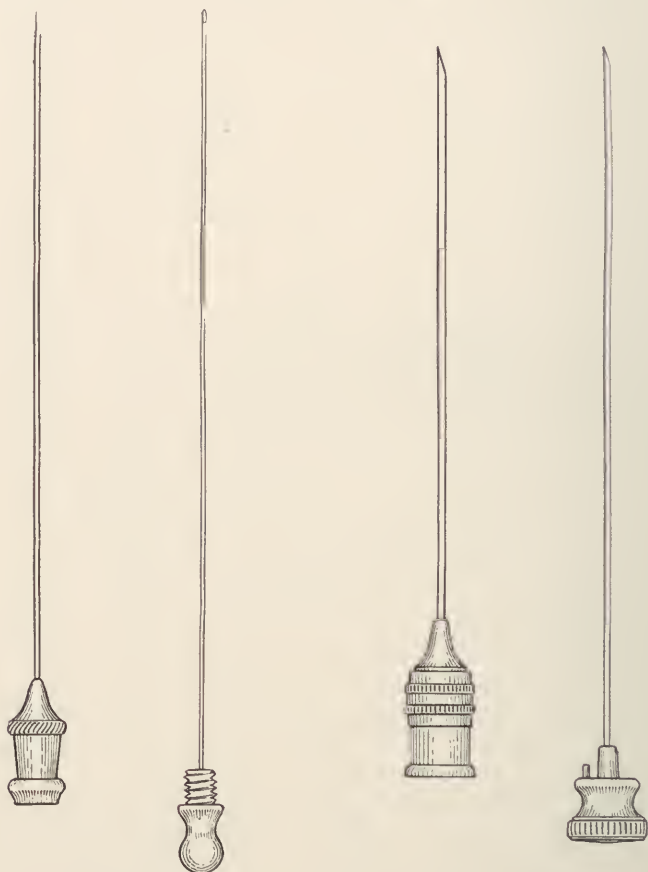


Fig. 13.—Various types of lumbar puncture needles.

needle, the only tabulated data available being by Quinke, who, however, cites only a few cases.

I measured the length of the needle in a series of several hundred cases, adopting the following procedure: When ready to remove the needle from the spinal canal after obtaining a good flow of fluid, I grasped the needle close to

TABLE I
MEASUREMENTS BY QUINCKE

AGE	DEPTH
1 $\frac{1}{3}$ years	2.0 cm.
7 “	2.5 “
	3.0 “
	3.0 “
	2.7 (3.5) cm.
	3.2 “
2 “	2.5 “
1 $\frac{1}{4}$ “	2.0 “
25 “	1.5 “
	6.0 “
	6.5 (4.7) “
39 “	5 plus “
22 “	5.2 “

the patient's skin between the thumb and index finger, pulled it out, and measured it from the point held by the fingers to the tip.

Table II gives the measurements of the needle made in children from four months to twelve years of age and Table III gives the measurements in adults of various ages. I included here but a few of the several hundred of measurements made. In cases in which the results were similar I tabulated but one measurement; in cases of the same age where the measurements were different several measurements are tabulated. In some cases the results of several measurements are given for the same patient to show the length of the needle at different punctures. As is seen from the table, the depth of the needle varies from 2.0 to 4.0 cm. in children up to twelve, and from 4.1 to 10 cm. in people over sixteen years of age. The variations in the adult may be attributed to several factors. Physique is one; the direction taken by the operator in inserting the needle is another, an oblique insertion naturally requiring a greater length of needle than a straight insertion. The location of the interspace is another factor, the higher the point of insertion, the greater being the length of the needle

TABLE II
MEASUREMENTS OF NEEDLE IN CHILDREN

NO.	AGE	LENGTH OF NEEDLE IN CM.
1	4 months	2.0
2	5 "	2.2
3	6 "	2.0
4	6 "	2.3
5	6 "	2.5
6	7 "	2.5
7	8 "	2.4
8	9 "	2.2
9	12 "	2.2
10	12 "	2.0
11	14 "	2.8
12	14 "	2.5
13	21 "	3.5
14	22 "	3.0
15	2 years	2.7
16	2 "	2.1
17	2 " 7 mos	2.4
18	3 "	4.0
19	3 "	2.0
20	3 "	2.8
21	3 "	2.3
22	4 "	3.2
23	4 "	2.9
24	4 "	2.8
25	5 "	3.2
26	6 "	3.0
27	7 "	4.0
28	8 "	3.5
29	8 "	3.5
30	9 "	3.7
31	9 "	3.4
32	9 "	4.0
33	9 "	3.8
34	10 "	3.6
35	12 "	3.2
36	12 "	3.6

introduced. Some clinicians use as the place of introduction the space between the second and third lumbar vertebrae, others the space between the first and second. It is also interesting to note that the length of needle inserted varies at different punctures in the same patient. This is due to the fact that the canal is quite wide and that fluid

TABLE III
MEASUREMENTS OF NEEDLE IN ADULTS

NO.	AGE	LENGTH OF NEEDLE IN CM.
1	16 years	5.4
2	20 "	4.8
3	25 "	5.0
4	26 "	5.3
5	27 "	5.8
6	29 "	4.9
7	29 "	5.5
8	30 "	5.6
9	30 "	4.5
10	30 "	5.4
11	30 "	5.2
12	30 "	5.8
13	30 "	5.6
14	31 "	5.5
15	31 "	10.0 (very fat)
16	32 "	5.1
17	33 "	4.1
18	33 "	5.1
19	34 "	5.1
20	34 "	5.2
21	34 "	4.5
22	34 "	4.6
23	35 "	5.7
24	35 "	4.8
25	35 "	5.5
26	36 "	4.1
27	37 "	5.3
28	37 "	5.5
29	37 "	5.9
30	38 "	5.0
31	39 "	7.0 (very fat)
32	40 "	6.0
33	40 "	6.4
34	40 "	4.9
35	40 "	5.0
36	40 "	6.4
37	42 "	5.0
38	43 "	6.3
39	43 "	4.5
40	44 "	4.9
41	44 "	5.8
42	44 "	5.5
43	45 "	5.5
44	46 "	4.9
45	48 "	4.9
46	48 "	5.3

(Cont'd p. 70)

TABLE III—Cont'd
MEASUREMENTS OF NEEDLE IN ADULTS

NO.	AGE	LENGTH OF NEEDLE IN CM.
47	48 years	5.5
48	52 "	5.2
49	53 "	5.1
50	53 "	10.0 (very fat)
51	53 "	6.0
52	54 "	5.2
53	55 "	5.3
54	55 "	6.7
55	57 "	5.4
56	57 "	5.6
57	60 "	4.1
58	60 "	5.9
59	60 "	6.0
60	60 "	5.9
61	61 "	5.9
62	65 "	8.0

may be removed whether the needle is near the anterior or near the posterior surface of the canal.

When the needle passes the dura, a snap is felt. The stylet should then be removed and the fluid allowed to run into the pressure apparatus or into tubes.

Failure to Obtain Fluid

There are times when no fluid can be obtained in spite of all efforts. Among the factors responsible for the failure to obtain fluid, the most important are the following:

1. The needle may not have been inserted far enough into the canal.

2. The needle may have been introduced too far into the canal. In such cases the material exuding from the intervertebral disc may clog up the needle.

3. There may be a thickening of the exudate in the spinal canal so that it cannot pass through the lumen of the needle. This happens occasionally in cases of suppurative meningitis.

4. There may be an absence of fluid at the lower part of the spinal canal. This may be caused by an obstruction,

by a tumor of the cord, or by blocking of the foramen of Magendie in hydrocephalus.

5. It may be due to a deformity of the vertebra such as occurs in advanced cases of tuberculosis of the spine, in rickets or spondylitis deformans.

If no fluid is obtained the stylet should be reintroduced into the needle to clear it of any particles that may be clogging the lumen, and it should then be withdrawn again. If there is still no sign of fluid the needle should be moved a little deeper or withdrawn slightly. If fluid is still not forthcoming, the needle should be removed and reintroduced one space higher. If after this procedure there is still no fluid an ethylchloride spray applied to the thigh may accelerate the flow. If after repeated trials no fluid escapes, one may ascertain whether the spinal canal has been reached by the following method: The first needle is left in its original position, and a second needle is introduced one space higher. A solution of sterile salt is injected into the higher needle. If the first needle is in the canal, the salt solution will flow out of it. When this happens it indicates that in all probability no fluid can be obtained because the canal is dry. As a rule one should be careful about pronouncing a puncture dry. A failure to obtain fluid may nearly always be attributed to some fault in the technic.

If the case shows symptoms of meningitis in spite of the fact that no fluid can be obtained by the spinal route, it may concern a basilar meningitis in which it often happens that the connection between the cranial and vertebral subdural space becomes clogged. In such a case ventricular puncture should be done. The technic of ventricular puncture will be described later.

The Presence of Blood in the Fluid

The presence of blood may be due to hemorrhage of the brain or to piercing of some vein of the plexus in the spinal

canal. If the presence of blood in the fluid is due to the striking of the plexus of veins, the exuding fluid has the color of fresh, venous blood. If it is due to cerebral hemorrhage, the blood in the fluid is dark red, and if the hemorrhage is one of long standing, clotted particles of blood may be seen clinging to the needle or coming out of the lumen.

✓ Pressure

The measurement of the cerebrospinal fluid pressure is very significant from the standpoint of diagnosis as it furnishes an almost immediate clue as to the existence of a pathologic condition. It should, therefore, be used in connection with lumbar puncture whenever possible.

Various types of apparatus have been described for the determination of the cerebrospinal fluid pressure. Quincke used an ordinary glass tube with a one-millimeter bore bent at the top, and an ordinary tape to measure the pressure; an arrangement like the one used by Quincke may be made at any laboratory by taking heavy glass tubing of one-millimeter bore, bending it at right angles below, and connecting it with hard rubber of one-millimeter bore to a tip fitting into an ordinary spinal puncture needle. The point to which the fluid reaches can be marked off and the height can then be measured on a slide or with a tape measure (Fig. 14). I used this arrangement for some time, but although it is of value, it is not accurate enough. The disadvantage of the Quincke apparatus lies in the fact that it takes too much time to attach the glass tubing to the needle. It frequently happens that the pressure of the fluid is so great that as soon as the stylet is removed from the needle, the fluid gushes out, and several cubic centimeters of fluid are lost before the tip of the pressure apparatus can be connected to the needle. In this way the real pressure value can not be ascertained, as it is known that once a few cubic centimeters of fluid are removed, the original cerebrospinal pressure is not maintained.

Several other types of apparatus have been described. One is by Kroenig, utilized principally for the purpose of withdrawing fluid from suspected cases of brain tumor.

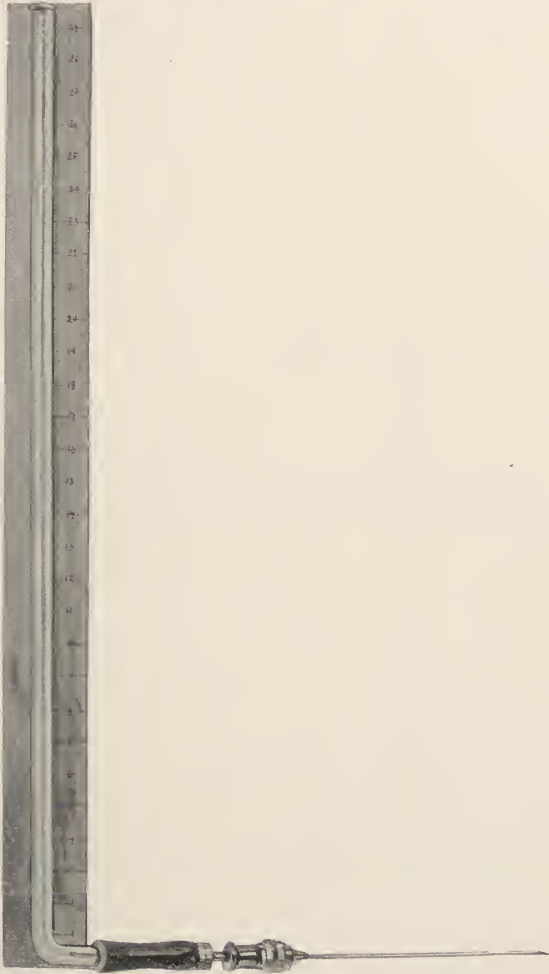


Fig. 14.—Modified Quincke apparatus for measuring the cerebrospinal fluid pressure.

The caliber of the measuring tube is so small, that it only takes a few drops to fill it, and when the column of fluid shows no oscillation, no more fluid should be withdrawn.

In my experiments on pressure I have been using an ap-

paratus which allows no loss of fluid and which has the added advantage of being simple.



Fig. 15.—Author's original spinal puncture needle and manometer; *A*, glass tubing in the needle; *B*, stopcock; *C*, upper projection of the needle into which the manometer is introduced; *D*, glass manometer.

The apparatus (Figs. 15 and 16) consists of a specially devised needle and a manometer.

The needle is the ordinary, medium-sized, spinal puncture needle with a short piece of glass mounting. The

glass tubing enables one to see whether the spinal canal has been reached with the first puncture. In the ordinary spinal puncture needle, one must withdraw the stylet entirely before one can see whether or not the spinal canal has been reached, thus running the risk of losing some fluid before the pressure can be measured. With the glass tubing on, one need only withdraw the stylet beyond the glass tubing, and if the spinal canal has been reached, the fluid withdrawn will be seen immediately through the glass. On the other hand, if no fluid makes its appearance, the stylet can be reinserted and another attempt made. The likelihood of breaking the glass observation tube on boiling the needle while sterilizing it is very slight. I have boiled needles, repeatedly, without ever breaking the glass.

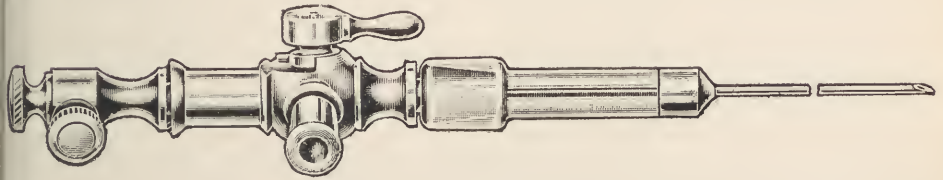


Fig. 16.—Author's improved spinal puncture needle.

The glass tubing may be slipped into the needle instead of being mounted, making possible the use of any form of spinal puncture needle. At the distal end of the glass tubing the needle has a three-way stopcock, the distal end of which is about three-fourths of an inch long. This length is required in order to allow space from the stopcock to the end of the needle so as not to lose any of the fluid as is the case when the valve of the stopcock is near the end of the needle. The stylet of the needle is long enough to reach from the distal to the proximal end of the needle.

The manometer consists of a long glass tube of one mm. bore which is inserted into the projecting end of the needle. The glass tubing is 800 mm. long as this was the highest pressure attained in any case, and for convenience sake, it is divided into two portions with a metal cap at

the top of the first portion so that the other one can be screwed on. This makes it convenient to carry the manometer in any small instrument case. Thick glass tubing is used for the manometer so that it does not break easily in handling. A metal ring is attached to the glass to measure the pressure. Of late I have also been using the mercury manometer devised by Fleischer (Fig. 17) with good results.

The needle (with the glass observation tube, the stopcock

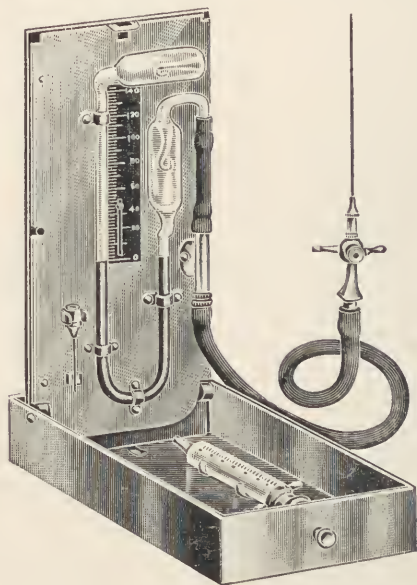


Fig. 17.—Fleischer's mercury manometer.

and its prolongation with the stylet inside) is introduced into the spinal canal. After a snap has been felt, so that one is reasonably certain that the subdural canal has been reached, the stylet should be removed to a point beyond the glass attachment. If fluid is seen in the glass tubing, the stopcock is turned at right angles so that the handle points upwards. The manometer is then attached and the stopcock turned so that the handle points opposite the manometer. The fluid will then rush into the manometer. When

the fluid has mounted to the highest point, the pressure is read. If no fluid is seen coming out when the stylet is removed beyond the glass tubing, the stylet should be reintroduced until the operator feels it is in the canal. It should then be removed beyond the glass and the measurement taken. The handle is now turned parallel to the needle and the fluid is collected in test tubes. The whole needle, including the glass attachment, stopcock, and prolongation is not any heavier than an ordinary medium-sized spinal puncture needle.

If no pressure apparatus is available, counting the drops and noting the force with which the fluid comes out from the needle will give a fair idea of the pressure, anything above ten drops per minute indicating an abnormal condition. I should like to emphasize once more that the pressure must be taken at the very beginning, as after several cubic centimeters of fluid have been removed, the pressure lets up and the determination then becomes practically valueless.

Collection of the Fluid

Some physicians collect cerebrospinal fluid in graduated medicine glasses, so as to be able to measure the exact amount. This method of collection, however, is not advisable as it is hard to keep the fluid sterile in a wide glass, and it is also hard to observe the characteristic sediment in cases of meningitis. It is therefore best to collect the cerebrospinal fluid in test tubes.

The test tubes in which the fluid is to be collected should be sterile and chemically clean. It is best to use tubes of uniform size. The glass of the tube should not be too thick and its opening should be stoppered with a cotton plug, unless special tests requiring a slow escape of CO_2 are to be made. For the sake of uniformity, the following method has been found useful in cases where a quantity greater than 5 c.c. of fluid is withdrawn.

Several drops of the fluid are allowed to run out of the needle to make sure that the fluid is free from blood. The entire amount is then collected into three tubes of uniform size. Into the first test tube is run in the first 2 c.c of fluid. This amount is used for several different examinations: (1) cytologic examination; (2) direct smear for microorganisms if the fluid is turbid; (3) cultures; (4) 1 c.c. for the permanganate test. The contents of the first tube should be examined immediately. If it cannot be examined immediately, the test tube with its contents should be placed in the incubator.

Into the second test tube, 3 to 5 c.c of fluid is collected. If the pressure is not increased the contents of this test tube should be used for the globulin tests, Wassermann and Lange. If the pressure is increased the test tube should be put into a tube rack for the formation of a pellicle. Care should be taken that the fluid is not disturbed.

If there is a large amount of fluid present, a third and fourth tube should be taken. Into the third tube should be run from 5 to 8 c.c. of fluid. This fluid should be used for (1) the second portion of the permanganate test; (2) the Ross-Jones, Noguchi and Pandey, and the sulphosalicylic-mercuric chloride tests; (3) Lange test; (4) Wassermann test; (5) sugar content; (6) chloride content; (7) centrifugation, for the examination of organisms.

Into the fourth tube should be run all the rest of the fluid desired for collection.

In normal cases where the pressure is not increased only 5 to 10 c.c. of fluid should be withdrawn. In all cases of increased pressure a greater quantity of fluid should be removed. In delirium tremens, 10 c.c. usually suffices to quiet the patient. In meningitis, 25 to 40 c.c. may be withdrawn on account of the greatly increased amount of fluid in the canal. Even in severe cases of meningitis, however, it is not advisable to remove more than 40 c.c. at one sitting on account of the danger of inducing shock. The

quality of the pulse is a good guide as to the amount of fluid to remove.

After the needle is withdrawn, the skin should be washed off with alcohol if iodine had been applied before the puncture, and collodion should be put on the wound. The patient should be put to bed immediately after the puncture to prevent headache or dizziness.

VENTRICULAR PUNCTURE

When no cerebrospinal fluid can be drawn by means of lumbar puncture and it is found urgent to obtain some for diagnostic or therapeutic purposes, as is the case when meningitis is suspected or present, or when it is desired to do both a spinal and ventricular puncture as is sometimes the case in hydrocephalus, cerebrospinal fluid may be obtained from the ventricles. The technic employed for a ventricular puncture in infants when the anterior fontanelle is not yet closed, is as follows:

The patient is wrapped in a sheet and placed on the back with the head close to the edge of the table. The region of the anterior fontanelle is shaved, washed with alcohol and ether, and painted with iodine. The needle to be used should be sterilized and all other necessary aseptic precautions should be taken. A short spinal puncture needle or an ordinary Luer needle may be used. The stylet should be left in the needle the same as in lumbar puncture, for if the stylet is removed brain tissue may clog the needle and prevent the flow of fluid. The head is held firmly by an assistant; and the needle is introduced into the anterior fontanelle. Any part of the fontanelle will answer the purpose, but it is best to introduce it in the horizontal line dividing the anterior fontanelle, $\frac{1}{2}$ to 1 cm. to one side of the median line. (Figs. 18 and 19.) The needle should be directed forward and outward. In normal infants the needle should be introduced $1\frac{1}{2}$ to $1\frac{3}{4}$ inches in depth. In

marked hydrocephalic infants fluid is obtained by introducing the needle $\frac{1}{4}$ to $\frac{1}{2}$ inch deep. After the desired amount of fluid is obtained, the needle is removed and collodion applied to the punctured surface. In infants with marked hydrocephalus where the frontoparietal suture is



Fig. 18.—Photograph showing ventricular puncture in infant by way of the anterior fontanelle. Dark circular spot shows needle in position. (Front view.)

wide open, the ventricle may be tapped through this suture (Fig. 20).

As in spinal puncture so also in ventricular puncture one may obtain bloody fluid. This is due to the piercing of a superficial vein in the scalp. If bloody fluid has been obtained the ventricular puncture should not be repeated for

several days. Ventricular punctures in infants are often followed by a rise in temperature. It does not, however, last more than a day or two.

In adults, cranial puncture is most generally made for therapeutic purposes, especially for the relief of intracranial pressure. It necessitates the use of a bore or a tre-



Fig. 19.—Photograph showing ventricular puncture in infant. (Side view.)

phine to get through the skull. The method used is that of Kocher, consisting of a trephine opening 2.5 cm. from the median line and 3 cm. in front of the coronal or frontoparietal suture. The needle is then passed inward and slightly backward for a distance of 4 or 5 cm. when the lateral ventricle is reached. The operation, in general, is a rather complicated one and calls for precision and careful

surgical technic. It should therefore be used only when absolutely necessary. The rule should be to do a lumbar puncture whenever possible, but when fluid can neither be obtained nor introduced by way of lumbar puncture, then ventricular puncture should be made, especially in the case of infants.

CISTERN PUNCTURE

The cisterna magna contains more cerebrospinal fluid than any other portion of the subarachnoid space. In laboratory animals this fact has been made use of for the purpose of removing cerebrospinal fluid. Quinke mentioned this method in connection with human beings, but considered it dangerous, because of the proximity of the cistern to the vital centers. Recently, however, the method was employed by a few observers with success. Cistern puncture may be resorted to in cases of spinal subarachnoid block for the purpose of withdrawing fluid, or for the introduction of serum, if all spinal and ventricular routes have failed. No one should, however, undertake a cistern puncture unless he has practiced the procedure on cadavers.

The following technic is described by Wegeforth, Ayers and Essick, the greatest exponents of the method.

The spinal puncture needle is introduced in the midline of the back of the neck just above the spine of the axis. The glabella and the upper edge of the external auditory meatus are found to be valuable structures for directing the course of the needle, for a plane passed through them and the point of insertion on the back of the neck will pass also through the occipito-atlantoid ligament. In thin persons palpation over the back of the neck often reveals a deep depression between the occipital protuberance and the spine of the axis, and with the tip of the finger the approximate position of the occipito-atlantoid ligament can be directly located. The distance necessary to insert the

needle in order to reach the cistern varies between 3 to 5 cm., the average distance being 4 cm.

The preparation and collection of the fluid, of course, is the same as in spinal or ventricular puncture.



Fig. 20.—Photograph showing ventricular puncture in infant by way of the left fronto-parietal suture. The white area in the center shows the bulging anterior fontanelle.

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CHAPTER IV

PHYSICAL AND CHEMICAL PROPERTIES OF NORMAL CEREBROSPINAL FLUID

The term "normal" as applied in the literature to cerebrospinal fluid is often misleading. The mere fact that cerebrospinal fluid has been removed from a living person is indicative of the presence of some abnormality of the nervous system that prompted the puncture. Often the bacteriologic and qualitative chemical tests on a given specimen of fluid are negative, yet quantitative chemical analysis will show an alteration in the chemistry or physical chemistry of the fluid. Many of the earlier data on normal cerebrospinal fluid have been based upon studies made on fluid obtained postmortem. Such fluid, however, can hardly be considered normal, for it has usually undergone marked chemical and physicochemical changes before examination. For instance, fluid removed postmortem has been shown by Myers to contain three and one-half times as much potassium oxide as fluid removed during life. Cotton and Ayer found a preponderance of endothelial cells in postmortem fluid. I also found a marked difference between fluid removed during life and after death. In the former case the fluid was slightly alkaline and in the latter, distinctly acid. "Normal" as applied to cerebrospinal fluid should, therefore, be considered merely as a relative term; the terms "nonmeningitic" and "nonlucetic" would perhaps be more accurate to designate fluid of cases in which there may be some pathologic condition of the nervous system, such as brain tumor, hydrocephalus or the like, but no involvement of the meninges.

In the discussion following in this chapter I shall state so far as possible whether the cerebrospinal fluid in ques-

tion was withdrawn during life or postmortem, and whether it was obtained by spinal or by cranial puncture. I shall also endeavor to indicate the diagnosis of the respective cases so that the reader may be able to form an opinion regarding the type of the fluid.

PHYSICAL PROPERTIES

Amount

The amount of fluid normally present in the ventricles and in the subarachnoid space has been variously stated. Contugno found between 125 and 156 c.c. in both; Magendie found between 62 and 372 c.c. According to Magendie, the normal amount of cerebrospinal fluid in a medium-sized man is 62 c.c. Of this amount, Magendie says, the ventricles contain from 20 to 30 c.c., and the subarachnoid space of the cord the greatest part of the remainder. Luschka found only 25 c.c. It may be interesting to note that although there is from 60 to 150 c.c. of cerebrospinal fluid present in the subarachnoid space and the ventricles, it is generally inadvisable and often impossible to remove more than 10 c.c. of fluid from a patient at one sitting.

Color

Normal cerebrospinal fluid is clear and colorless, provided no blood has been removed with it during the puncture. The fluid does not change color upon standing if it is corked with a cotton plug, unless, of course, it has become contaminated by bacteria or moulds, in which case the fluid becomes turbid.

Lack of Sediment

Normal cerebrospinal fluid shows no pellicle or sediment of any kind. This is because of the fact that the cell content, as well as the protein content, is very small, and fibrin

is either entirely absent or present only in very small traces. The lack of sediment is helpful in differentiating normal or nonmeningitic fluid from fluid in cases of meningitis, especially tuberculous, in which the diagnosis is difficult because of the clearness of the fluid.

Pressure

Observations on the pressure of normal cerebrospinal fluid have given various results in the hands of different workers. Magendie found that the pressure of the cerebrospinal fluid is positive. Falkenheim and Naunyn claim that it is necessary for the maintenance of the blood circulation of the brain that the cerebrospinal fluid remain at a certain pressure and they estimate the pressure under normal conditions to vary between 50 and 200 mm. of water (4 to 16 mm. of mercury) for a child one month to one year of age, with a correspondingly higher pressure for an adult. Quincke gives 40 to 60 mm. of water as the normal pressure for children, and 150 for adults; Adamkiewicz gives 80 to 100 mm. of water, and Sicard gives 200 as the normal pressure. Many factors are responsible for these discrepancies, the most important of them being the type of the pressure apparatus, the insertion of the needle, the portion of the fluid, the age of the patient, the position of the patient, the position of the head, the respiratory movements, and such external factors as coughing, sneezing and crying.

(a) Different pressure apparatus give different pressure values. In some forms of apparatus fluid is lost and therefore too small values are obtained. (Cf. Chapter III.) The position of the needle is also responsible for variation in pressure. A deeper insertion of the needle into the canal gives a higher pressure than a slight insertion, and vice versa.

(b) Different portions of the fluid give different pres-

sure readings, the first portion showing a higher reading than the subsequent ones.

(c) Age also plays a part in the pressure of the fluid. Quinke found pressure in children to be less than that in adults. He gives 40 to 60 mm. water as the pressure in children, and 150 mm. water as the pressure in adults. I also found the pressure to be lower in children than in adults. My figures showed a pressure variation of from 45 to 90 mm. water in children in a quiet, recumbent posture and 130 to 150 mm. water in adults.

(d) The position of the patient during puncture has a marked influence on the pressure, the pressure in the sitting position being much higher than in the recumbent position. Kroenig found the pressure in the lying posture to be 120 mm. of water and in the sitting posture 410 mm. of water. Cotton and Salz found the normal pressure in the recumbent position to be 200 to 230 mm. of water and in the sitting position to be 400 to 420 mm. water. I found the normal pressure in the recumbent position in children under ten to vary between 45 and 90 mm. of water and in the sitting position to vary between 150 and 230 mm. of water. In adults, in recumbent position the pressure varied between 130 and 150 and in the sitting position between 200 and 250.

(e) Flexion of the head on the chest lessens the pressure and extension of the head raises the pressure, the difference between the two varying from 150 to 230 mm. of water.

(f) Magendie commented on the effect of the respiratory movements on the pressure of the fluid. He observed that the cerebrospinal fluid showed movements corresponding to the respiration, the pressure falling during inspiration and rising during expiration. This observation has been confirmed by many workers. I have observed it frequently. The variation between inspiration and expiration, however, is small, the difference averaging from 10 to 15 mm. of water.

(g) The relation between the pressure of the cerebrospinal fluid and the pulse beat was pointed out by Falkenheim and Naunyn.

(h) Coughing, crying, sneezing or any other strain may increase the pressure from 50 to 100 mm. of water.

Summarizing, it may be said that the normal pressure of the cerebrospinal fluid is influenced by many factors. As a general rule, however, the pressure varies from 45 to 90 mm. in children, and from 130 to 150 mm. in adults.

TABLE IV

CEREBROSPINAL FLUID PRESSURE IN NORMAL INDIVIDUALS EXPRESSED IN
MILLIMETERS OF WATER

AUTHOR	ADULT		CHILD	
	LYING	SITTING	LYING	SITTING
Quinke	150		40-60	
Adamkiewicz		80-100		
Kroenig	125-150	410		
Cotton and Salz	200-300	400-420		
Boveri	170-200			
Levinson	130-150	200-250	45-90	150-230

These figures are for the recumbent position. They are very much higher for the sitting position. The withdrawal of several cubic centimeters of cerebrospinal fluid lessens the pressure temporarily, but in a very short time it returns to normal. So it frequently happens that when two punctures are made in one day, the pressure is found to be the same in both cases.

Hemorrhage from any part of the body lessens the cerebrospinal fluid pressure markedly.

Weed and McKibben and later Foley and Putnam showed that it is possible to reduce the cerebrospinal fluid pressure and diminish the bulk of the brain by injecting a hypertonic solution into the blood stream.

The mechanism underlying cerebrospinal fluid pressure is not well known. Many factors have been made responsible for the cerebrospinal fluid pressure. Of these factors

only one is known to play a great rôle, and that is blood pressure. Of this, the venous pressure plays the greatest rôle. Whatever raises the venous pressure within the skull also raises the cerebrospinal fluid pressure and vice versa.

Specific Gravity

The specific gravity of normal cerebrospinal fluid varies between 1.001 and 1.008. Hoppe found the specific gravity in a case of spina bifida to be 1.001 and in one case of hydrocephalus to be 1.005. Halliburton found the specific gravity of normal fluid to be 1.007 to 1.008, and Kafka found it to vary between 1.002 and 1.008. Zdarek gives the specific gravity of normal cerebrospinal fluid as 1.0078, Polányi gives it as 1.012, 1.007 and 1.005. Mestrezat found it to be 1.0076, and Nawratski found it to be 1.0073 to 1.008. In a series of nonmeningitic cerebrospinal fluids examined by the pycnometer I found the specific gravity to vary between 1.0034 and 1.0070.

CHEMICAL COMPOSITION

In spite of the large amount of work done on the chemical composition of the cerebrospinal fluid, there are many fundamental questions pertaining to the chemistry of this fluid that have not yet been answered. The reason that our information regarding the chemistry of cerebrospinal fluid is not as definite and as accurate as it might be, is that the amount of fluid one is obliged to work with under normal conditions is usually so small (5 to 10 c.c.) that it hardly permits a complete quantitative analysis.

It is but recently that microchemical methods have been devised for body fluids, and even now, with improved methods, it is hardly possible to make an entire quantitative analysis on one specimen of normal cerebrospinal fluid. This scarcity of fluid necessitates working on one chemical

substance at the time or the use of a mixture of fluids for the determination of the various chemical constituents, a procedure adopted by Mestrezat. One can readily see that data gathered in this way cannot be very accurate, especially since the chemical character of the fluid is affected by such factors as the condition of the patient, and the age of the fluid. It is surprising to note, however, that with all of the drawbacks some of the chemical determinations of the very early investigators still hold good, particularly the determinations of the organic matter, and of the amount of the total solids and chlorides.

I shall present here data obtained from the literature, following the experiments as far as possible in chronologic order to show the evolution of chemical methods as applied to cerebrospinal fluid. I shall give a table at the end of the discussion showing the results of the work by various authors on the chemistry of the cerebrospinal fluid.

Early Investigations

One of the earliest determinations of the chemical composition of cerebrospinal fluid was that of Lassaigne who examined the cerebrospinal fluid of a horse after death. The fluid was obtained for the chemist by Magendie. The analysis gave the following composition per 100 parts:

Water	98.180
Osmazome	1.104
Protein	0.033
Sodium chloride	0.610
Sodium bicarbonate	0.060
Phosphate and traces of calcium carbonate	0.009

Lassaigne could not find any soluble phosphates in the liquor.

The same author examined the cerebrospinal fluid of an old woman and found the following per 100 parts:

Water	98.564
Osmazome	0.474
Protein	0.088
Sodium and potassium chloride....	0.801
Animal matter and free calcium phosphate	0.036
Sodium carbonate and calcium phos- phate	0.017

Among the early workers in this field was Hoppe. He made a chemical analysis in two cases of spina bifida and three cases of internal hydrocephalus. In one case of spina bifida, he removed 22 to 35 c.c. of cerebrospinal fluid at a sitting. (The author unfortunately does not give the method he employed in the removal of the fluid.) He found the fluid very alkaline. (Here again the author does not say what indicator he used, or how long after removal of the fluid from the body, he examined it). On heating, the fluid became slightly turbid, but on addition of acetic acid, flocculi appeared. The fluid reduced copper oxide and gave the following quantitative results in grams per 1000:

	FIRST PUNCTURE	SECOND PUNCTURE	THIRD PUNCTURE
Protein	1.62	2.64	2.46
Water extractive	0.70	0.35	0.42
Alcohol extractive }	9.57	2.48	2.23
and soluble salt }		7.52	8.21
Insoluble salt	0.25	0.15	0.28
<hr/>			
Giving—			
Dry substance	12.51	13.12	13.28
Water	987.49	986.88	986.72

From the second case of spina bifida the author obtained 500 c.c. of cerebrospinal fluid in the first puncture, and 435 c.c. in the second puncture. The reaction of the fluid in this case was also stated to be alkaline. On boiling, very little, if any, turbidity occurred. On the addition of acetic acid slight flocculency occurred. Quantitative analysis showed the following in grams per 1000:

	FIRST PUNCTURE	SECOND PUNCTURE
Protein	0.25	0.55
Extractives	2.30	2.00
Soluble salts	7.67	7.20
Insoluble salts	0.45	0.45
	<hr/>	<hr/>
Dry Substance	10.67	10.20

One case of hydrocephalus in a five-month-old girl gave Hoppe the following in grams per 1000: protein 0.70, extractives 1.57, soluble salts 7.67, insoluble salts 0.53, giving dry substance 10.47.

Another case of hydrocephalus gave Hoppe the following in grams per 1000: protein 11.79, alcohol extractives 0.84, water extract 0.48, soluble salts 7.54, insoluble salts 0.35, and dry matter 20.99. However, from the author's description of the fluid of the last case, which he says was of a greenish yellow color and showed a large sediment, absence of sugar and numerous cells, it is evident that the case was one of meningitis.

Halliburton also was one of the first to study the chemical composition of cerebrospinal fluid. He found no coagulation of the fluid at 56° C. and no fibrin on the addition of serum or fibrin ferment. He found further that practically all the protein present in the cerebrospinal fluid was precipitated by saturation with magnesium sulphate. The analysis of cerebrospinal fluid in a number of cases gave Halliburton the following results in parts per 1000:

	CASE 1. FEMALE—AGE 19	CASE 2. CHILD—AGE 11 DAYS FIRST TAPPING	CASE 3. CHILD—AGE 13 WEEKS FOURTH TAPPING
Water	989.75	989.877	991.658
Solids	10.25	10.123	8.342
Proteins	0.842	0.602	0.199
Extractives	9.626	0.631	3.028
and			
Salts		7.890	5.115

RECENT INVESTIGATIONS

Some of the earlier work has been corroborated and a number of new facts have been obtained recently in connection with the chemical composition of cerebrospinal fluid. I shall discuss here only the most important chemical constituents of the fluid.

Total Solids

Mestrezat found the total solids of normal cerebrospinal fluid to vary between 1.065 and 1.100 gms. per 100 c.c. of fluid. Various other authors found the total solids to vary between 1.200 to 0.876 gms. per 100 c.c. The specimen I examined contained between 1.398 and 1.631 gms. of total solids per 100 c.c. of fluid, the water varying between 98.602 and 98.369 per 100 c.c. I should like to point out once more that I prefer to speak of nonmeningitic and nonlucetic fluid rather than of normal fluid, as I believe that very few fluids brought to any laboratory are normal.

Inorganic Matter

Mestrezat made a complete analysis of the ash of normal cerebrospinal fluid. He found the total ash to vary between 0.850 to 0.900 gms. per 100 c.c. Sodium oxide averaged 0.4346, potassium oxide averaged 0.025 gms. The ratio of sodium to potassium was 17.30 to 1; magnesium oxide averaged 0.0050, calcium oxide 0.0095, iron oxide 0.0002, nitrates 0.0009, sulphates 0.0010, phosphates (P_2O_5) 0.0030, chlorides varied between 0.728 to 0.740 gms. per 100 c.c.

In my work on the inorganic constituents of the cerebrospinal fluid the phosphates averaged 0.0041 gms. per 100 c.c. The chlorides varied between 0.60 and 0.74 gms. per 100 c.c. as is evident from Table V. The carbonates varied with the time the fluid had been standing after removal from the body. The longer it stood before examination the less CO_2 it contained. In fluid examined immediately after

withdrawal from the body, the CO_2 varied between 0.110 gm. and 0.124 gm. per 100 c.c. In fluid examined five to six hours after it had been removed from the body, the CO_2 varied between 0.098 gm. and 0.106 gm. per 100 c.c. Table VI shows the amount of CO_2 in volume per cent obtained in some fluids.

TABLE V
CHLORIDES IN NONMENINGITIC FLUID

NO.	DIAGNOSIS	CHLORIDES (IN GMS. PER 100 C.C.)
1	Psychosis	0.74
2	Alcoholic psychosis	0.72
3	Alcoholic psychosis	0.60
4	Meningism	0.72
5	Pneumonia	0.60
6	Psychosis	0.68
7	Psychosis	0.70
8	Tertiary lues	0.75
9	Chorea	0.70

TABLE VI
TOTAL CARBONATE OF NONMENINGITIC CEREBROSPINAL FLUID AND ITS
RELATION TO THE H-ION CONCENTRATION

NO.	DIAGNOSIS	PH	TOTAL CARBONATE IN VOLUME PER CENT
1	Dementia Precox	7.4	58.75
2	Psychosis	7.4	55.72
"	"	7.7	51.52
3	Cerebrospinal Lues	7.5	55.72
"	"	7.6	54.83
4	Psychosis	7.4	57.54
"	"	8.1	50.47
5	Tubes	7.4	63.68
"	"	8.1	54.08
6	Chorea	7.5-7.6	63.0
"	"	8.1	52.48
7	Encephalitis	7.7	51.3

Organic Constituents

The organic constituents of cerebrospinal fluid attracted the attention of investigators even earlier than did the inor-

ganic constituents. Among the subjects investigated were the total amount of organic matter, the organic or permanganate index, the amount of protein, the type of protein, the amount of urea, amino acids, sugar and cholesterol. Of late, the nitrogen constituents of cerebrospinal fluid have received considerable attention. The subject includes total nitrogen, nonprotein nitrogen, urea nitrogen, and creatinine nitrogen.

Organic Matter and Organic Index

The total organic matter of cerebrospinal fluid varied in Mestrezat's cases between 0.175 to 0.265 gms. per 100 c.c. The organic or permanganate index as determined by the Meyerhofer method (described in detail in Chapter VII) varied in my cases between 1.3 to 1.8 in the first tube and between 1.1 to 1.7 in the second tube as is evident from Table VII.

TABLE VII
THE PERMANGANATE INDEX IN NONMENINGITIC FLUID

NO.	DIAGNOSIS	PERMANGANATE INDEX		
		FIRST TUBE	SUBSEQUENT TUBES	
1	Typhoid	1.8	1.6	1.7
2	Pneumonia	1.3	1.3	
3	Pneumonia	1.4	1.2	1.0
4	Tetany	1.3	1.2	
5	Epilepsy	1.3	1.1	
6	Grippe	1.5	1.4	

Protein

The amount of protein varied in Mestrezat's cases between 0.013 to 0.030 gms. in 100 c.c. of fluid. Various authors found between 0.02 to 0.07 gms. in 100 c.c. In my series of nonmeningitic fluids the protein varied between 0.0130 and 0.0470 gms. per 100 c.c.

The question of the type of protein in normal fluid is not settled yet. The early investigators claimed that albumin is entirely absent from normal fluid. Mestrezat found that although globulin is the predominant constituent of the protein in cerebrospinal fluid, serum albumin is also pres-

ent in normal fluid. In one case the globulin was 0.013 gm. and the serum albumin 0.004 gm. per 100 c.c.

Kirsehenbaum and I, using the Howe method for the distribution of protein in cerebrospinal fluid (work to be published), found no albumin present in normal or non-meningitic and nonluetic fluid. The only exception to it was found in fluid from two cases of epilepsy, where small amounts of albumin were present.

Sugar

As early as 1852, Deschamps and Bussy described the presence of a copper-reducing substance in cerebrospinal fluid. This was soon corroborated by numerous other workers. However, the character of this substance has

TABLE VIII
SUGAR CONTENT IN NONMENINGITIC AND NONLUETIC CASES

NO.	DIAGNOSIS	SUGAR CONTENT
1	Alimentary Intoxication	0.116
2	Pneumonia with meningism	0.108
3	Insanity	0.108
4	Uremia	0.067
5	Insanity	0.058
6	Insanity	0.048
7	Otitis Media	0.032
8	Erysipelas	0.144
9	Renal Insufficiency	0.048
10	Pneumonia and meningism	0.032
11	Pneumonia	0.088
12	Brain tumor also right ovarian cyst	0.116
13	Cerebral spastic paralysis	0.06
14	Hydrocephalus	0.104
15	Insanity	0.118
16	Hematogenous Jaundice	0.12
17	Epilepsy	0.068
18	Encephalitis	0.048

(Cont'd p. 98)

TABLE VIII—Cont'd

SUGAR CONTENT IN NONMENINGITIC AND NONLUETIC CASES

NO.	DIAGNOSIS	SUGAR CONTENT
19	Cerebellar tumor	0.072
20	Brain tumor	0.068
21	Multiple sclerosis	0.148
22	Localized encephalitis recovered.	0.140
23	Acidosis (?)	0.104
24	Normal	0.086
25	Normal	0.09
26	Normal	0.106
27	Normal	0.064
28	Normal	0.088
	Blood sugar—0.088	
29	Normal	0.108
30	Normal	0.064
31	Normal	0.07

been made the subject of a great deal of discussion. Quinke, Comba, Friedenthal, Panzer and others considered it a dextrose. Halliburton, however, supported by Mathien, Gauthies and others, expressed the view that the reducing substance was pyrocatechin. Langstein thought that a portion of the reducing substance was galactose and Dubos believed that it was a xanthine body. Recent investigations have settled this controversy, the phenylhydrazin, the fermentation test, and the polariscope definitely proving its identity as a dextrose. Even Halliburton now admits that this reducing substance is a dextrose.

The data on the amount of sugar in cerebrospinal fluid are quite numerous. Jaksch found it to vary between 0.06 to 0.08 gms. per 100 c.c. Hopkins found it to vary between 0.060 to 0.075 gms. per 100 c.c. Schloss and Schroeder found it between 0.054 to 0.139 gms. per 100 c.c. In my cases the sugar varied between 0.032 to 0.148 gms. per 100 c.c. (Table VIII).

Nitrogen

The total nitrogen varied in Mestrezat's series between 0.0196 to 0.0198 gms. per 100 c.c. In my cases the total

TABLE IX
TOTAL NITROGEN IN NONMENINGITIC AND NONLUETIC FLUID

NO.	DIAGNOSIS	TOTAL NITROGEN (GMS. PER 100 C.C.)
1	Mental defect	0.032
2	Pneumonia	0.022
3	Meningism	0.0464
4	Otitis	0.024
5	Epilepsy	0.012
6	Pneumonia	0.0218

nitrogen varied between 0.0218 to 0.0464 gms. per 100 c.c. (Table IX).

The nonprotein nitrogen varied in Leopold and Bernhard series between 0.0176 to 0.026 gms. per 100 c.c. and in my series between 0.0126 and 0.0388.

Urea nitrogen varied in Leopold and Bernhard series between 0.007 to 0.0135 gms. per 100 c.c. Kahn found between 0.014 to 0.033 gms. per 100 c.c. and Folin found between 0.006 to 0.020 gms. per 100 c.c. In my cases the urea nitrogen varied between 0.006 to 0.020 gms. per 100 c.c.

There has been some confusion in the literature between the figures of urea nitrogen and urea. It is obvious that the urea figures will be higher than the figures for urea nitrogen.

Creatinine was found by Seham and Nixon to vary between 0.00045 to 0.0022 gms. per 100 c.c. Leopold and Bernhard found it to vary between 0.0007 to 0.0015 gms. per 100 c.c. In my cases the values ran between 0.00093 to 0.0014 gms. per 100 c.c.

Other Organic Constituents

Cholesterol is absent in normal fluid, or present only in minute traces. The same is true of lactic acid. Acetone is absent from normal fluid. Amino acids are stated by various authors to be present between 0.0010 to 0.004 gms. per 100 c.c.

The chemical methods that have been found of diagnostic value will be described in detail in Chapter VII. The methods employed for research purposes are the same as those employed for blood, a detailed description of them being found in the various text books on physiological chemistry.

Comparison of Blood and Cerebrospinal Fluid Chemistry

It is interesting to compare the chemical composition of the cerebrospinal fluid with that of other body fluids, notably blood, lymph, and aqueous humor. In comparing the chemical composition of the cerebrospinal fluid with that of the blood we find that they both contain practically the same constituents, and that some of the constituents are present in the same amounts in both. This is particularly true of nonprotein nitrogen sugar and urea. I often found nonprotein nitrogen and sugar to be present in the same amounts in both the fluid and in the blood. Cullen and Ellis found a difference of less than 2 mg. per 1000 c.c. in the amounts of urea in the fluid and the blood, in 63 per cent of their determinations. The urea content of the fluid varied from 22 to 46 mg. and that of the blood serum between 20 to 42 mg. per 100 c.c.

The other chemical constituents, on the contrary, are present in much smaller proportions in the fluid than in the blood. The protein in the fluid varies between 0.013 and 0.047 whereas that in the blood plasma varies between 6.95 and 7.76 per cent. The calcium content of the fluid, according to Halverson and Bergeim, is only one-half that of the blood, the calcium in the fluid being 0.005 gm. per 100 c.c., while that in the blood plasma or serum is 0.01 per 100 c.c. Table XII shows the chemical constituents of the cerebrospinal fluid and the blood.

TABLE XII

 COMPARISON OF THE CHEMICAL AND PHYSICOCHEMICAL COMPOSITION
 OF BLOOD SERUM AND CEREBROSPINAL FLUID

(Expressed in grams per 100 c.c.)

	BLOOD		CEREBROSPINAL FLUID	
Water	90.88	92.0	98.3	99.66
Dry matter	9.11		1.63	1.09
Organic matter	8.25		0.175	0.265
Protein	6.7	8.7	0.013	0.047
Amino acids	0.006	0.008	0.0010	0.004
Sugar	0.10	0.12	0.032	0.148
Cholesterol	0.150	0.275	Trace	
Total nitrogen	2.65		0.0218	0.0464
Nonprotein nitrogen	0.020	0.035	0.0126	0.0388
Urea nitrogen	0.010	0.019	0.006	0.020
Creatinine nitrogen	0.00145	0.00220	0.00045	0.00220
Chlorides (As sodium chloride)	0.060	0.70	0.60	0.75
Specific gravity	1.040	1.065	1.0034	1.0070
Freezing point		0.56	0.56	0.58
H-ion concentration	P _H 7.4	7.6	7.4	7.6
Alkalai reserve	45-63%	CO ₂	45-63%	CO ₂

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CHAPTER V

PHYSICOCHEMICAL PROPERTIES OF NORMAL CEREBROSPINAL FLUID

There is no line of scientific investigation where so many factors enter into the results obtained as in physicochemical determinations. Temperature, barometric pressure and especially the length of time the fluid has been standing before it is examined count a great deal. So it comes that while the chemical data found in the literature of several years ago are in the main confirmed by newer investigations, some of the older physicochemical data are found incorrect when newer methods are used, and when the various factors influencing physicochemical findings are taken into consideration. Especially is this true with regard to the reaction of the cerebrospinal fluid and the alkali reserve.

Specific Gravity

The specific gravity of normal cerebrospinal fluid to which I have already referred in the discussion of the physical properties of normal cerebrospinal fluid, belongs also in a discussion on physicochemical properties of the fluid, since specific gravity forms the basis of many physicochemical constants. The specific gravity varied in my cases between 1.0034 and 1.0070, and according to other authors, it varies between 1.001 and 1.008.

Viscosity

Polányi found the viscosity to vary between 1.020 and 1.027 at a temperature of 38° C., taking the viscosity of water as 1. I examined the viscosity of several specimens of cerebrospinal fluid, by means of the Ostwald apparatus, and found it to vary between 1.0424 and 1.0489 compared to water.

Conductivity

Polányi examined the conductivity of the cerebrospinal fluid of hydrocephalus and found it to be 0.01136 ; 0.01280 ; 0.01527 ; and 0.01452 at 20° C. (Formula $\frac{1}{\text{Ohm} \times \text{Cm.}}$).

My examination gave the conductivity as 0.01513 , 0.01365 , and 0.01513 at 25° C.

Surface Tension

Polányi found the surface tension to be 7.35, 7.15, 7.16 and 7.20 dynes at 20° C. Ascoli-Izar found it to vary between 101 to 105 stalagmometer drops, which is slightly less than water.

Freezing Point

Grenet found the freezing point of normal cerebrospinal fluid to be -38° to -56° C. Quinke found it to be -56° to -75° . Polányi found it to be -566° , -570° , -678° , -583° . Mott found it to be -51° to -56° . Mestrezat found the average to be -576° , the extremes between -57° and -59° . My findings showed the freezing point to vary between -56° and -58° . Here also the interval between the removal of the cerebrospinal fluid from the body, and the time of the examination is a great factor; although the variation in the freezing point on standing is not nearly as much as is the case with the H-ion concentration, or with the alkali reserve.

Refractometric Index

Polányi found the refractometric index to be 1.3499 at 23° C., 1.33516 at 21° C., 1.33579, at 20.3° C., and 1.33554 at 20° C.

Crystallization

I evaporated a number of specimens of cerebrospinal fluid, after precipitating and filtering off the protein. The

resultant crystals (Figs. 21 and 22) resembled those of sodium chloride (Fig. 23) in most respects. The crystals dissolved in water very easily.

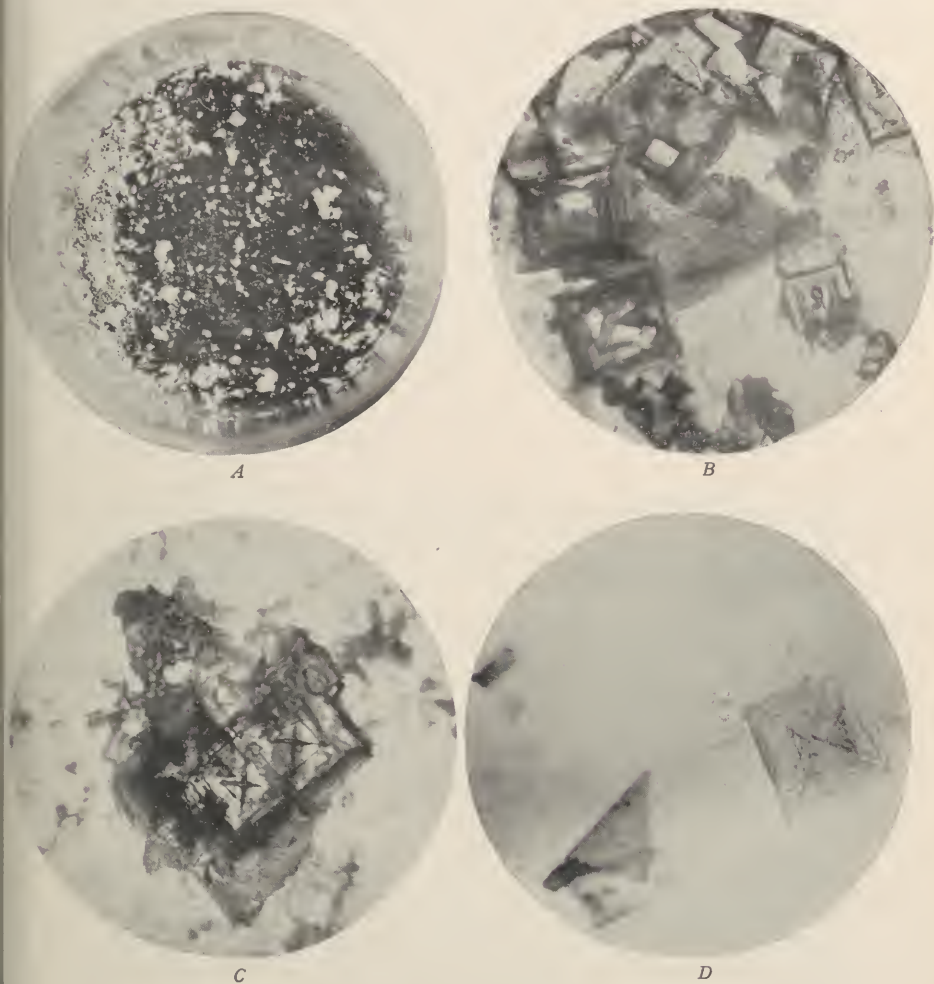


Fig. 21.—Crystallization of nonmeningitic cerebrospinal fluid.

- A.* Crystals obtained after the protein has been removed from the fluid by precipitation and the filtrate evaporated on steam bath. (Natural size.)
- B.* Same fluid showing the crystals. Magnified 24 times.
- C.* Clump of crystals of same fluid. Magnified 45 times.
- D.* Single crystal. Magnified 45 times.



Fig. 22.—Crystals of evaporated nonmeningitic cerebrospinal fluid. (Magnified 24 diameters.)

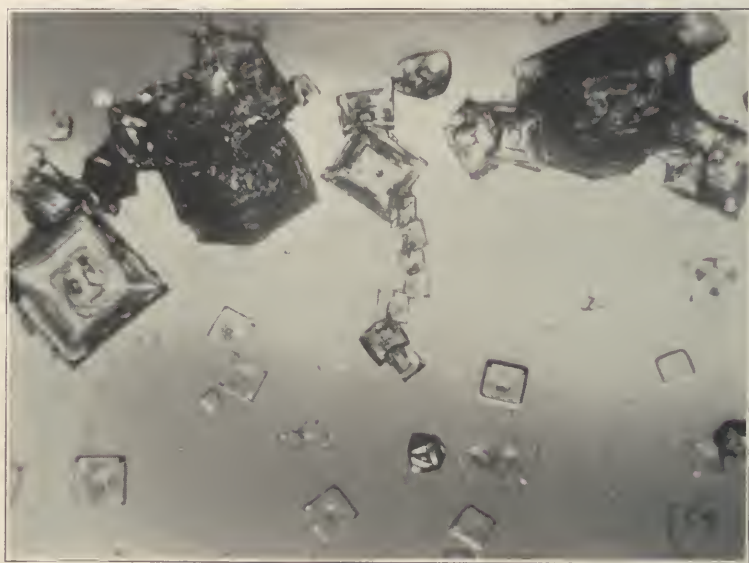


Fig. 23.—Crystals of sodium chloride in a 1 per cent solution of dextrose. (Magnified 24 diameters.)

Reaction of Normal Cerebrospinal Fluid

All through the older writings, the statement is found that the cerebrospinal fluid is alkaline in reaction, the alkalinity being given as a rule as half that of the blood. Cavazzani examined the fluid of two cases of hydrocephalus, and found it neutral in reaction. Concetti found the fluid alkaline three times, and weakly alkaline four times. Von Jaksch found the alkalinity to equal 20 c.c. of $n/10$ acid solution.

Kafka used $n/10$ HCl and cochineal as an indicator, and found that on an average, 20 c.c. of acid was necessary to neutralize 100 c.c. of fluid. According to Mott, the alkalinity of the fluid corresponds to 0.1 per cent of sodium hydroxide.

Of late, the entire conception of the reaction of body fluids has changed due mainly to the work of Michaelis, Sörensen, Henderson and Van Slyke. The reaction of body fluids is now spoken of in terms of hydrogen and hydroxyl ions, which is expressed either in the terms of hydrogen-ion concentration, or in terms of P_H , the latter term indicating the negative exponent of the hydrogen-ion concentration, for instance $P_H 7.1 = 1 \times 10^{-7.1}N$. The H-ion concentration can be determined in a number of ways, the most important of which are the compensation method of Michaelis or of Hildebrandt, and the indicator method of Sörensen. Practically all of these methods have been used recently for the study of the cerebrospinal fluid. The results, however, have not been uniform. Bisgaard examined the fluid against a borate mixture, 5.7 plus HCl, and found that the fluid was more acid than the borate mixture. Polányi determined the H-ion concentration of one fluid drawn from a case of hydrocephalus, by the compensation method with the use of the Farkas-Szilisch electrode. He found the H-ion concentration to be 9.084×10^{-8} . Hurwitz and Tranter, who used the Levy Rowntree-Marriott standards, found the P_H of normal fluids

to vary between 8.15 and 8.30 with an average of 8.26, this being somewhat lower when the fluid was dialyzed, the average then being 8.11. Weston found the dialyzed fluid to vary between 7.9 and 8.3 with an average of 8.12. Felton, Hussey and Bayne-Jones, using the Levy-Rowntree-Marriott method, found the reaction of cerebrospinal fluid to vary between P_H 7.7 to 7.9 when examined immediately after removal from the body and P_H 8.7 when examined after the fluid has stood for some time.

TABLE XIII

H-ION CONCENTRATION OF NORMAL CEREBROSPINAL FLUID BY OTHER AUTHORS

AUTHOR	METHOD EMPLOYED	P_H		REMARKS
		FRESH	OLD	
Cavazzani	Tartaric acid	Neutral Interval of standing not indicated.		2 cases of hydrocephalus.
Concetti		Alkaline 3 times, weakly acid 1 time. Interval of standing not indicated.		
Myers	Litmus	Neutral or faintly alkaline		
Bisgaard	Phenolphthalein	Less than 8.1		
Kopetzky	Litmus	Less than 8.0		
Turner	Phenolphthalein	Acid		{ Fluid in stoppered bottles retained acidity Fluid in unstoppered bottles became alkaline
Polányi	Farkas-Szilisch electrode		9.0	
Hurwitz and Tranter	Levy-Rowntree-Marriott method		8.15 8.30 average-8.1	
Weston	Levy-Rowntree-Marriott method		79-8.3 average-8.12	
Felton, Hussey and Bayne-Jones	Levy-Rowntree-Marriott method	7.7-7.9	8.6	

I have examined the H-ion concentration in over four hundred normal cerebrospinal fluids, or to be more accurate, fluid from cases that proved to be nonmeningitic in character. The series included cases of nephritis, gastrointestinal intoxication, pneumonia, paresis, alcoholic psychosis, dementia precox, brain tumor, epilepsy and many other conditions. I used the methods of Michaelis and Hildebrandt for the determination of old fluids and the Levy-Rowntree-Marriott method, or an indicator corresponding to this method, in fresh fluid. I found that when the fluid is examined immediately after its withdrawal from the body, the H-ion concentration, expressed in terms of P_H ranges from 7.4 to 7.6. In only two cases have I found an H-ion concentration of fresh fluid to be 7.7. However, if the fluid has been standing a short while, the reaction changes very quickly toward the alkaline side. As a rule, standing half an hour changes the reaction to a P_H of 7.5 to 7.6; standing one hour changes the reaction to a P_H of 7.7; standing two hours changes it to 7.9 or 8.0. From two hours on, the change in the reaction toward the alkaline side is rather small, some fluids changing in twelve hours to 8.1, and remaining at this concentration no matter how long it stands; other fluids changing to 8.3 or even 8.6 in course of twenty-four hours or longer.

In Table XIV, I give the H-ion concentration in some of my cases showing average results, indicating the method used by the letters a, b, c; "a" represents the gas-chain method, "b" the alkalized phenolphthalein compared to the Sörenson standards, and "c" the Levy-Rountree-Marriott indicator compared to the standard colorimetric tubes. A typical change in the H-ion concentration is illustrated in the curve shown in Fig. 24. The results obtained by phenolphthalein compared to the Sörenson standards, are often marked with an additional + and - signs. This means that P_H of the cerebrospinal fluid was higher or lower than

the figure given, but how high or how low was not determined.

These findings have been so constant that I believe we can account for the high P_H obtained in normal cerebrospinal fluid by the authors quoted. They examined the fluid after it had been standing for some time, which naturally gave a very low H-ion concentration, or a high P_H . Interesting in this connection is the work of John Turner who not only knew of the high H-ion concentration

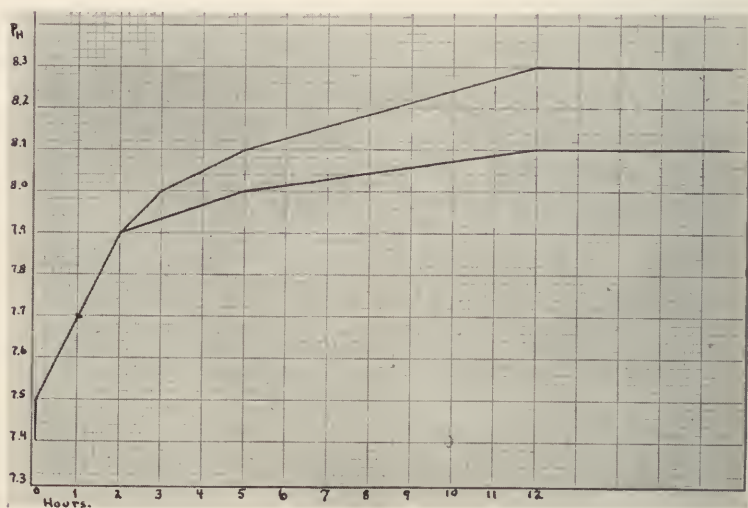


Fig. 24.—Average change in the H-ion concentration of nonmeningitic fluid on standing.

of the fluid, but was also aware of the fact that the concentration changes on standing. To quote him:

“In all the cases of this series and in twenty examined fifteen years ago, I have obtained an alkaline reaction (and not amphoteric) to litmus paper, but with phenolphthalein the great majority have an acid reaction. The degree of acidity, however, is in many cases very slight. A very faint pink solution of phenolphthalein was poured into two small beakers, so that the tint in both was similar in looking down at them as they stood upon a porcelain

slab. A little of the fluid was then added to one beaker and generally the pink color was immediately discharged. I found that the fluid left unstoppered in my room, where gas is constantly burning, rapidly becomes alkaline, whereas similar fluid in stoppered bottles retained its acidity, and that in my later examinations where this source of fallacy was recognized and excluded, the results tend more and more to be uniformly acid with phenolphthalein."

I have endeavored to find the factors that are responsible for the changes taking place in the H-ion concentration of nonmeningitic cerebrospinal fluid. I found that when I put a part of the cerebrospinal fluid right after its withdrawal from the body into a desiccator containing twenty per cent sodium hydrate, and allowed it to remain in the desiccator from ten to thirty minutes, the acidity of the fluid was greatly decreased, the P_H being in a very short time 7.7 to 7.9.

This shows that the removal of CO_2 from the fluid causes a decrease in the H-ion concentration of the fluid. To make certain, however, that the increase in the P_H of the cerebrospinal fluid is entirely due to CO_2 , I performed the following experiment. I divided a fluid into two portions: one portion I corked tightly after its removal from the body, and coated with a layer of paraffin, and the other portion I left in a nonsol glass tube. The two portions of the fluid were examined twenty-four hours later. I found that the fluid which had been corked very tightly retained the original H-ion concentration, giving a P_H of 7.4 to 7.6 in twenty-four hours; while the fluid that had been left in a cotton plugged test tube gave a P_H of 8.1 or higher in twenty-four hours, which is the ordinary change taking place in cerebrospinal fluid. This shows that the decrease in the H-ion concentration in the cotton-plugged tube was not due to formation of ammonia or other alkaline substance, but to the loss of CO_2 from the fluid into the air. I have furthermore shown that when the tube containing

TABLE XIV

H-ION CONCENTRATION OF NONMENINGITIC SPINAL FLUID

CASE	DIAGNOSIS	P _H			
		Immediate	½ Hour	1 Hour	2 Hours
1	Little's disease.....
2	Tetanus.....
3	Pneumonia.....
4	Gastro-enteritis.....
5	Brain tumor.....
6	Endarteritis.....
7	Typhus.....
8	Brain tumor.....
9	Tic.....	8.0 (b)
10	General paresis.....	8.0 (b)
11	Delirium tremens.....
12	General paresis.....
13	Psychosis.....
14	Tubercle of brain.....	7.4 (b)
15	Juvenile paresis.....	7.4 (b)
16	Alcoholic.....	7.4 + (b)
17	General paresis.....	7.4 + (b)
18	Alcoholic.....
19	Paranoia.....	7.5 (c)
20	Epilepsy.....	7.4 (c)
21	Epilepsy.....	7.5 (c)
22	C. Sp. Lues ?.....	7.9 (c)
23	Paresis.....	7.7 (c)
24	Psychosis.....	7.7 (c)
25	Psychosis.....	7.5 (c)
26	Psychosis.....	7.6 (c)
27	Psychosis.....	7.5 (c)
28	Psychosis.....	7.5 (c)
29	Brain tumor.....	8.0 (c)
					8.0 (b)
30	Pneumonia.....
31	Alcoholic.....	7.4 (c)	7.4 (c)	7.5 (c)	7.9 (c)
32	General paresis.....	7.4 (c)
33	Psychosis.....	7.7 (c)
34	Psychosis.....	7.5 (c)
35	Alcoholic.....	7.4 (c)
36	Psychosis.....	7.4 (c)
37	Psychosis.....	7.5 (c)
38	Alcoholic.....	7.5 (c)
39	Alcoholic.....	7.4 (c)
40	General paresis.....	7.5 (c)
41	Psychosis.....	7.4 (c)	7.6 (c)
Mixture		7.4 (c)	7.8 (c)
42	Psychosis.....	7.4 (c)
43	Psychosis.....	7.5 (c)
Mixture	Psychosis.....	7.4 (c)
Mixture	
44	Poliomyelitis.....	7.7 (c)
Mixture	General paresis.....	7.4 (c)
45	
46	Pneumonia.....	7.7 (c)
Mixture		7.4 (c)
47		7.4 (c)
48	Psychosis.....	7.5 (c)
49	Meningism.....	7.5 (c)
50	Poliomyelitis ?.....	7.6 (c)

(Continued on p. 115.)

fluid is corked tightly, but some space is left between the fluid and the cork, there will be some change in the H-ion concentration of the fluid, the H-ion decreasing slightly

TABLE XIV—Continued

H-ION CONCENTRATION OF NONMENINGITIC SPINAL FLUID

[illegible]

* Corked.

although not nearly as much as the fluid standing in the cotton-plugged tube (Table XVI) (Fig. 25). I have also measured the total carbonates in fresh and old fluid and

TABLE XV

CHANGES IN H^+ CONCENTRATION ON REMOVAL OF CO_2 BY EXPOSURE TO ALKALI IN DESICCATOR

CASE	FLUID DRAWN	PH IM-MEDI- ATELY	EXPOSED TO ALKALI	EXPOSED TO AIR	EXAMINED	PH.
190	6:55 p. m.	7.4	12 minutes	7 minutes after 20 minutes exposure to alkali	7:07 p. m.	7.7-7.8
190	6:55 p. m.	7.4	20 minutes		7:15 p. m.	7.8
190	6:55 p. m.	7.4	20 minutes		7:22 p. m.	7.8-7.9
190	6:55 p. m.	7.4	27 minutes	38 minutes after 27 minutes exposure to alkali	7:55 p. m.	7.8-9
190	6:55 p. m.	7.4	20 minutes	13 hours	11:22 a. m.	8.1
188	7:03 p. m.	7.4	10 minutes		7:13 p. m.	7.7-7.8
188	7:03 p. m.	7.4	30 minutes	3 minutes	7:33 p. m.	7.8
188	7:03 p. m.	7.4	30 minutes		7:36 p. m.	7.8
186	7:45 p. m.	7.4	6 minutes		7:51 p. m.	7.6-7.7
186	7:45 p. m.	7.4	25 minutes		8:10 p. m.	7.9

found it to run parallel with the H -ion concentration as shown in Table VI. To show further that ammonia, even if absorbed from the air, is a negligible factor, I made the following experiment: A fluid was divided into two portions, one of which was exposed to ammonia-free air in a

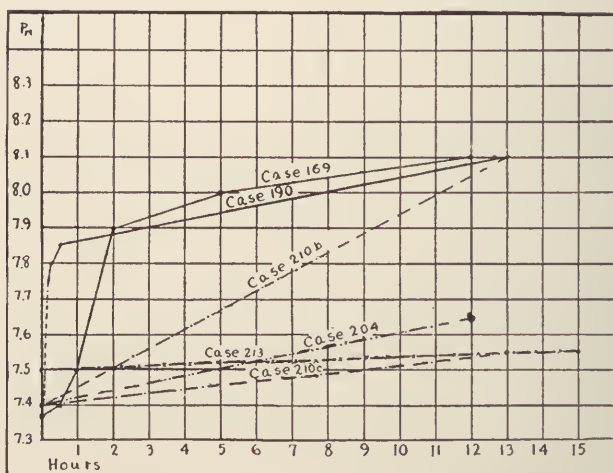


Fig. 25.—Change in H^+ concentration of nonmeningitic fluids on standing at room temperature under various conditions. Case 169. Plugged with cotton. Case 190. Immediately after withdrawal, exposed to CO_2 free air in desiccator (dotted line) and later left with cotton plug. Case 210b. Plugged with cotton; Case 210c, the same fluid as b, but corked with a cork—a few bubbles at the top. Case 204. Six c.c. tube, half filled, and tightly corked; cotton plugged fluid was same as Case 210b (8.1). Case 213. Almost perfectly sealed with cork, without any air bubble above the fluid.

TABLE XVI

II + CONCENTRATION OF FLUIDS STANDING IN CORKED TUBES

N U M - B E R	A G E	D I A G N O S I S	I N T E R V A L	S T O P P E R E D W I T H	P _H
Mixture 210a	27	Alcoholic	Immediately		7.4
	38	Alcoholic	Immediately		7.4
210b	27	Alcoholic	13 hours	Cotton	8.1
	38	Alcoholic			
210c	27	Alcoholic	12 hours	Paraffined cork (few bubbles below cork)	7.5-7.6
	38	Alcoholic			
211a	43	Alcoholic	Immediately		7.5
	46	Alcoholic			
211b	43	Alcoholic	12½ hours	Cotton	8.1
	46	Alcoholic			
211c	43	Alcoholic	12½ hours	Paraffined cork	7.5-7.6
	46	Alcoholic			
211d	43	Alcoholic	15½ hours	Paraffined cork replaced after 3 c.c. removed for exam. at 8:10, leaving 3 c.c. space in 6 c.c. tube.	7.6
	46	Alcoholic			
212	55	Alcoholic	4 minutes		7.4
b	55	Alcoholic	15 hours	Paraffined cork	7.5-7.6
c	55	Alcoholic	15 hours	Cotton	8.2
d	55	Alcoholic		Cotton	7.9
213	39	Alcoholic	2 minutes		7.5
b	39	Alcoholic	15½ hours	Paraffined cork	7.5-7.6
218	1 yr.	Pneumonia	Immediately		7.5-7.6
b	1 yr.	Pneumonia	47 hours	Paraffined cork	7.5-7.6
c	1 yr.	Pneumonia	47 hours	Cotton	8.2
204	46	Pulmonary tuberculosis	15 minutes		7.4
	42	Alcoholic	10 minutes		
	38	General paresis	Immediately		
b	38	General paresis	12 hours	Cotton	8.1
c	38	General paresis	12 hours	Paraffin; left 3 c.c. space above volume of liquid.	7.6-7.7
205	29	Alcoholic	11 minutes		7.4
	34	Alcoholic	8 minutes		
	36	Alcoholic	Immediately		
b	36	Alcoholic	12 hours	Cotton	8.1
c	36	Alcoholic	12 hours	Paraffined; 1 c.c. of space left on top of fluid	7.5-7.6

desiccator, and the other left at the ordinary laboratory temperature. After thirty minutes I examined the two fluids for their H-ion concentration and found it to be the same in both cases, showing that the usual decrease in the H-ion concentration of a fluid is not due to absorption of ammonia from the air.

When we compare H-ion concentration of normal cerebrospinal fluid with that of the blood, we find that they are both the same. The H-ion concentration of the blood also ranges between a P_{H} of 7.4-7.6 immediately after being removed from the body.

Alkaline Reserve

I determined the alkaline reserve or the amount of CO_2 present in the cerebrospinal fluid as bicarbonate, by means of the Van Slyke alkaline reserve apparatus. Table XVII shows the alkaline reserve in nonmeningitic fluid:

TABLE XVII
ALKALINE RESERVE OF NONMENINGITIC CEREBROSPINAL FLUID

NO.	DIAGNOSIS	ALKALINE RESERVE
1.	Tabes	56.5
2.	Poliomyelitis	45.7
3.	Uremic coma	52.0
4.	Meningism	47.5
5.	Chorea	63.0
6.	Dementia precox	58.75
7.	Psychosis	55.72
8.	Cerebrospinal lues	55.72
9.	Psychosis	57.54

The above shows that the alkaline reserve of nonmeningitic cerebrospinal fluid varies between 45.7 and 63.0, the greatest number running between 52 and 57% of CO_2 bound by the cerebrospinal fluid at 0° temperature, at 760 barometric pressure, which is about the same as the alkaline reserve of blood.

TABLE XVIII
PHYSICO-CHEMICAL CONSTANTS OF NORMAL CEREBROSPINAL FLUID

CONDITION	AUTHOR	SPECIFIC GRAVITY	VISCOSITY	FREEZING POINT	CONDUCTIVITY	SURFACE TENSION	REFRACTIVE INDEX	H-ION CONCENTRATION IN TERMS OF PH.	ALKALINE RESERVE
Hydrocephalus	Polányi	1.012 (15° C.) 1.003 (20° C.)	1.020 1.027	0.566 0.678	0.01136 0.01527	7.15 7.35	1.33516 (20° C.)	9.0	
Normal	Mestrezat	1.0076		0.57 0.59					
Nonmeningitic	Levinson	1.0034 1.0070	1.0424 1.0489	0.56 0.58	0.01365 0.01513			7.4-7.6	45.7-63% of CO ₂

BIOCHEMICAL PROPERTIES

The data on the biochemical properties of normal cerebrospinal fluid are conflicting in nature. Up to date most of the biochemical properties reported on have been negative in nature, but it is possible that with more accurate methods positive biochemical properties may be found.

Catalase

In a series of fluids examined by Becht and myself, by means of the special apparatus described by Becht, no catalase or only a negligible amount was found in normal cerebrospinal fluid. (Table XIX.)

TABLE XIX
CATALASE FINDINGS IN NONMENINGITIC FLUID

DIAGNOSIS	INTER- VAL	READ- ING	CELLS PER C.M.M. AT TIME OF CATALASE DETERMINATION	OTHER TESTS
Chorea	½ hr.	0, 0	4	0
Microcephalus	½ hr.	0, 0	4	0
Meningism	2 days	2, 2	2	Globulin slightly positive
Normal	2 days	3, 2, 2	4	0
Scarlet fever	4 days	5, 5	0	0
and diphtheria				
Epilepsy	1½ hrs.	2, 2, 2	1	0
Brain tumor	1 hr.	4, 4, 4, 4	50 lympho- cytes	0
Cerebral hem- orrhage	19 hrs.	2, 2	2	Globulin positive

Amylase

Toison and Lenoble found that the cerebrospinal fluid of hydrocephalics possesses amyolytic power. Cavazzani reports the same. Galletta, however, found this to be true in only two out of eleven cases examined. Mestrezat found no amyolytic power in normal cerebrospinal fluid or very slight traces of it.

Proteolase

Link and Pollack report finding a peptolytic enzyme in normal cerebrospinal fluid. In three cases of hydrocephalus and one case of spina bifida examined for the presence of pepsin or trypsin Halliburton found no trace of either. Miller found no proteolytic enzyme or antienzyme in normal cerebrospinal fluid.

Galletta found a fat-splitting enzyme in three of seven cases. Clerc found none.

Glycolytic Ferment

Cavazzani found glycolytic ferment in the cerebrospinal fluid. However, neither Panzar, Lewandowsky, nor Mott could find the presence of any glycolytic ferment.

Alexin

Normal fluid contains no alexin.

Hemolysin

Normally no hemolysin is found in the fluid.

Toxicity

Normal fluid is not toxic, compared to pathologic fluid which is toxic.

Bactericidal Action

The question as to whether normal fluid has a bactericidal action has not yet been settled.

CYTOLOGY

The study of the cell content and of the cell elements of the cerebrospinal fluid was inaugurated in France by Ravut, Sicard, Nagoette and Vidal in 1901, and has since been recognized as a very important phase of the study of the cerebrospinal fluid.

The exact number of cells in normal cerebrospinal fluid is a matter on which authorities who have worked with the fluid do not agree. Fuchs and Rosenthal found 0 to 2 cells per c.mm. in normal fluid, Rehm found 1 to 5 and even 6 to 9, and Gemmerich found 8 cells in the fluid of one healthy person. There are others who give the number as 5 to 20 per c.mm. The reason for the wide discrepancy is the fact that different investigators have employed different methods in determining the number of cells. There are some who count the cells in the centrifuged fluid, using a certain amount of fluid in a graduated centrifuge tube and taking one drop of the sediment on a slide (the so-called French method), and others who count the cells in counting chambers. It is easy to see how these two methods will give entirely different results, the difference being at times as high as 50 or 60 per cent. Even those who count the cells in a counting chamber, get variations in their results due to the type of chamber they use. The Fuchs-Rosenthal chamber, for instance, gives a smaller percentage of error than the ordinary leucocyte counter. The greatest source of errors responsible for the discrepancy of findings by various authors however, is the admixture of blood in the cerebrospinal fluid, for no matter how clear the fluid may look there may be some blood cells obtained by the passage of the needle through the tissue, which would in turn result in enormous errors, when figured out as their number per c.mm. In addition to the above factors, the stain may account for the difference in the reports of the various authors.

I found the number of cells in normal fluid to be between 1 and 6 per c.mm. I have, therefore, adopted this number as an arbitrary standard, anything above 6 cells per c.mm. being suspicious, and anything above 10 cells per c.mm. being indicative of some pathologic condition of the central nervous system, although not every increase in cells means an inflammation of the meninges. Some cases showing an

increased cell count in the cerebrospinal fluid are due merely to an irritation of the meninges. Of course I make certain that the cerebrospinal fluid contains no blood to begin with.

Fischer claims that the result obtained in the cell count of fluid obtained by lumbar puncture is not indicative of the cell count in the cerebrospinal fluid contained in the ventricle of the brain. This, however, has been found by Nonne not to be true. The cell content in the fluid of the lumbar region, and that of the ventricle are found to run parallel to each other. I have found that the cell content in the different portions of the cerebrospinal fluid does differ, the first tube containing more cells than the subsequent fluid. I believe that this may be due to a contamination of blood cells in the first portion of the fluid. In this connection, it is interesting to point out that one author advises shaking the patient from side to side before doing a lumbar puncture, in order to stir up the cells and distribute them evenly which, of course, is very absurd.

Type of Cell

Normally, no red blood cells are found in the fluid, the cells in the fluid always being leucocytes. The normal type of leucocyte in cerebrospinal fluid is the small lymphocyte, which is the size of a red blood cell or slightly smaller or larger than the red blood cell. The nucleus of the lymphocytes of normal cerebrospinal fluid is round or slightly oval. It is seldom irregular. The nucleus fills up the largest part of the cell leaving a very small cell body. No granules can be detected in the cells, as a rule. The nucleus stains intensively with methyl-violet, while the cell body does not.

Large lymphocytes do occur in normal fluid but not very frequently. It has been observed that there very seldom exists a combination of large and small lymphocytes in

the same specimen of fluid that gives no other pathologic findings. Large lymphocytes, however, always should make one think of some diseased condition of the central nervous system.

The origin of the cells in the cerebrospinal fluid is not fully determined. The cells in normal fluid would seem to be of hematogenous origin as they are small lymphocytes with occasional large forms which are also found in the blood.

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CHAPTER VI

PATHOLOGIC CEREBROSPINAL FLUID

Cerebrospinal fluid reacts to all processes that affect the central nervous system. It also reacts to systemic processes which increase the permeability of the meninges to certain chemical metabolic products.

With this in view the changes in cerebrospinal fluid may be looked upon as due to one of three causes:

1. Simple irritation of the meninges.
2. Infection of the meninges.
3. New growth of the meninges.

Irritation of the meninges may be produced (1) by the retention in the blood and later in the cerebrospinal fluid of chemical substances such as urea, sugar, and chlorides; (2) by the action of toxins; (3) by inflammation or pressure of the brain tissue, or (4) by inflammation of structures adjacent to the cranial cavity.

An example of irritation of meninges by chemical substance may be found in uremia and diabetes. In these diseases, especially in their advanced stages, the fluid is increased in amount and in pressure, sugar is present in large amounts in the fluid of diabetes and protein, urea and chlorides are often increased in uremia. The cell content, however, is usually not increased.

An example of irritation of the meninges by toxin is found in some cases of pneumonia or influenza. The fluid is increased in amount and in pressure, but the cells and globulin are not increased. There may be a slight increase in the cells and in the globulin in cases of pneumonia. This occurs when the irritation of the meninges has persisted for a few days.

Another example of irritation of the meninges is seen in cases where the brain tissue proper is inflamed or shows marked pressure changes. In encephalitis, the meninges show some irritative changes. The cerebrospinal fluid in turn is increased in amount and in pressure. The cells are slightly increased as is the globulin. In brain tumor and brain abscess, the same condition holds good, in their early

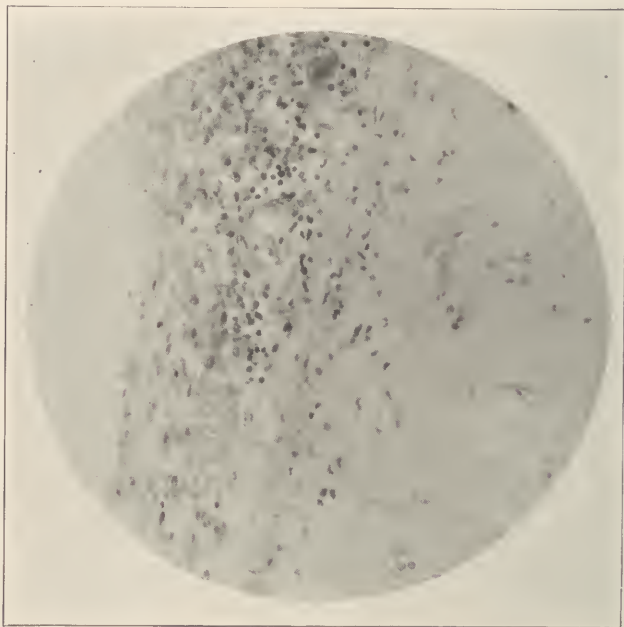


Fig. 26.—Irritation of the pia associated with abscess of the brain. The pia, at the left, is slightly edematous, its nuclei are swollen, and at the upper margin of the picture are a few lymphocytes and a dilated blood vessel. Hematoxylin and eosin. X230.

stages (Fig. 26). However, since no pathologic condition is stationary, the irritation of the meninges, if prolonged, may turn into a real inflammation of the meninges, in which case we have the characteristic gross and microscopic changes of meningitis postmortem (Fig. 27) and the characteristic meningitic changes of the cerebrospinal fluid.

Not only does inflammation or pressure of the brain

produce an irritation of the meninges; even inflammation of structures external to the cranial cavity may irritate the meninges, as long as the structures are adjacent to cranial cavity. This is seen in many cases of otitis media and mastoiditis.

Irritative changes of the meninges are termed serous meningitis by some and meningism by others.

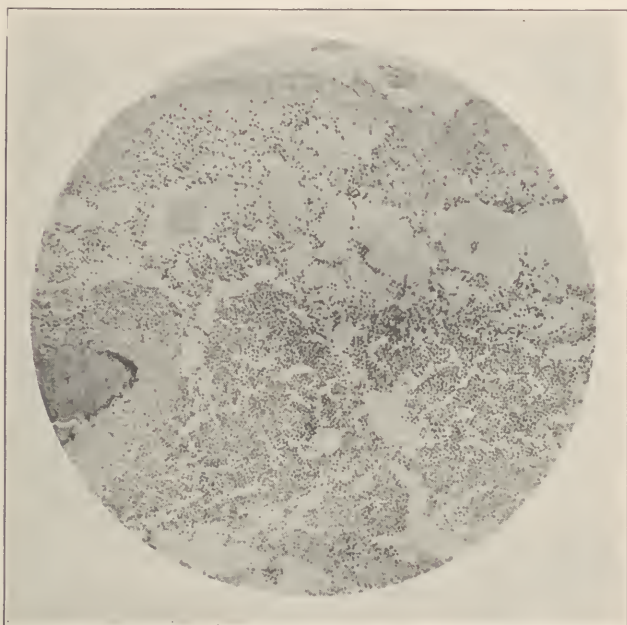


Fig. 27.—Acute purulent meningitis secondary to abscess of the brain. At the left is an artery whose wall is infiltrated by leucocytes. Hematoxylin and eosin. X80.

The pathogenesis of meningism, I believe, may be explained on simple mechanical grounds. If one keeps in mind that the cerebrospinal fluid is greatly influenced by the blood pressure inside of the cranium, it can easily be seen that any irritation reaching the brain either by general circulation, as in pneumonia, for instance, or through adjacent structures, such as in otitis media, will accelerate the circulation of the blood in the cranium, thus raising the

cranial blood pressure and therefore also producing an increase in the cerebrospinal fluid pressure.

Because there is no change in the reaction of the fluid, and only an occasional change in the chemical composition of the fluid, the meningeal symptoms subside immediately after the withdrawal of the extra quantity of the fluid in the subdural cavity or as soon as the principal disease in

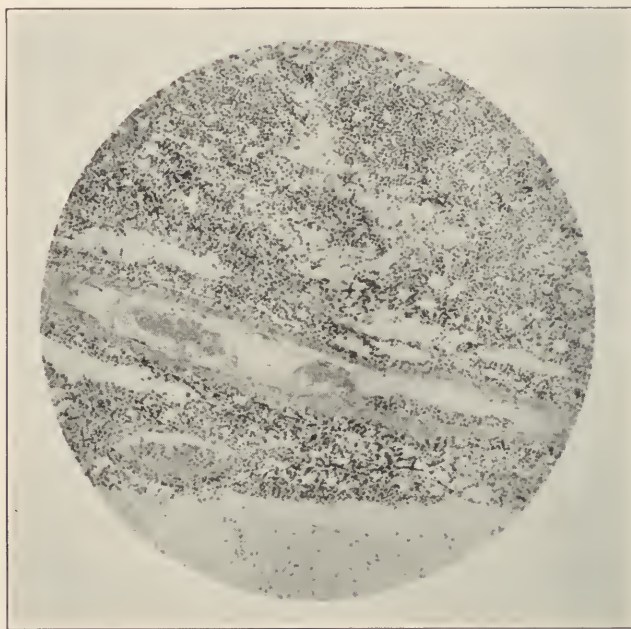


Fig. 28.—Acute meningococcus meningitis. The brain, below, is covered by a thick layer of purulent exudate. Hematoxylin and eosin. X95.

some other part of the body develops; for instance it is noticed often that as soon as the pneumonia is fully developed the meningeal symptoms disappear. This, I believe, can be explained by the assumption that as soon as the pneumonia is fully developed the large volume of blood is removed from the brain and transferred to the lungs, thus decreasing the cranial blood pressure, and consequently decreasing the cerebrospinal fluid pressure.

That this is the case seems evident from the cases of meningism in which no spinal puncture has been done, and still the symptoms subside, the fluid in the subdural cavity being absorbed as soon as the volume of blood in the cranium is decreased.

Infection of the meninges may be chronic, such as luetic, or acute such as the various acute meningitides. The changes in the fluid due to infection of the meninges are

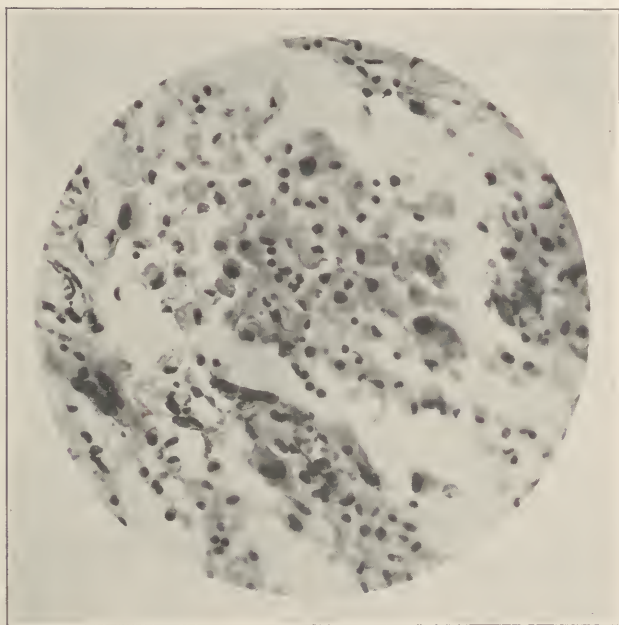


Fig. 29.—Acute meningococcus meningitis. A group of swollen endothelial cells. Hematoxylin and eosin. X300.

usually physical, chemical, cytologic, bacteriologic and immunologic. The changes may appear singly or in various combinations. They are a reflection of, and correspond to the changes in the meninges found on postmortem examinations. So are endothelial cells found both in the fluid of meningococcus meningitis and in the meninges (Figs. 28 and 29) and so do lymphocytes predominate in the fluid of tuberculous meningitis and in the meninges (Fig. 30).

Just how bacteria may enter the cerebrospinal fluid is still a matter of controversy. There are two ways in which they can make their entrance: one is through the circulation and the other is by direct continuity from the nose or from the ears. For a long time it was thought that the attack of the meninges in meningococcus meningitis or in poliomyelitis was by way of the lymphatics of the nasal mucous membrane, the bacteria passing through the cribri-

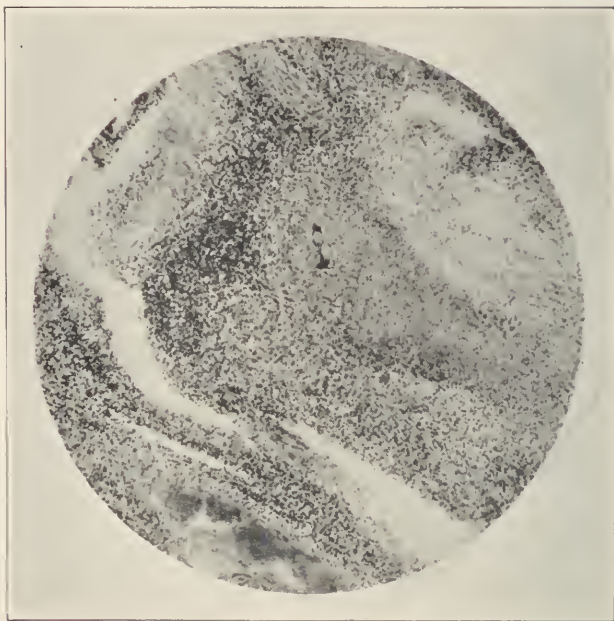


Fig. 30.—Tuberculous meningitis. At the lower margin is an area of caseation necrosis. In the middle is a tubercle with a giant cell. The pia is diffusely infiltrated by lymphocytes. Hematoxylin and eosin. X95.

form plate of the ethmoid directly into the meninges. However, the fact that the meningococcus in many cases may be cultivated directly from the blood in the early stages of meningitis, and that arthritis and iridochoroiditis often complicate and even precede meningitis, would make one believe that the meningeal infection is most frequently hematogenous. The recent work of Herrick on meningeal infection in man and of Austrian on experimental menin-

gitis speak in favor of the septicemic nature of meningococic invasion.

In tuberculous meningitis the infection hardly ever reaches the meninges directly from the nose. It is usually part of a general miliary tuberculosis of which the meningitis is a terminal process. From the work of Albrecht and Ghon, we know that the primary process of tuberculosis usually takes place in the lung, and gives rise to an enlargement of the hilus glands, which in time either become retrogressive with calcification, or go on to a general miliary tuberculosis. According to this explanation, what happens in tuberculous meningitis, then, is first a tuberculous infection in the lung tissue proper; second, an infection of the hilus glands; and third, an invasion of the meninges by way of the blood. It takes some time before the protective wall of the meninges is broken through by the tubercle bacilli, but they finally break through and infect the meninges. That tuberculous meningitis is a part of a miliary tuberculosis is seen on autopsy, miliary tubercles being found in the lungs, liver, and spleen in all cases.

The pneumococci act much like the tubercle bacilli and meningococci in their relation to meningitis. Not every pneumonia, it is true, produces a pneumococcus meningitis but almost every pneumococcus meningitis is the result of a pneumococcus septicemia. Some observers claim that they have found pneumococci in the cerebrospinal fluid in uncomplicated pneumonia, although there is no apparent reason why pneumococci in the fluid should produce meningitis in one instance and not in another. The nervous system is the master system of the body, and Nature has provided it with protection by surrounding it with cerebrospinal fluid and with three layers of meninges, one of which, the dura, is especially heavy and firm. In addition, Nature also protects the meninges with the heavy walls of the skull and spine and in spite of the fact that the nervous system is a delicate system, and that the cerebrospinal

fluid is not microbicidal it is not easy for bacteria to gain access to either.

In certain cases the meningococci and other bacteria find their way into the cerebrospinal fluid through the cribriform plates of the ethmoid. The nasal mucous membrane may harbor pneumococci and streptococci, meningococci and influenza bacilli, and it is conceivable that when the system is in a low state of resistance, the bacteria may enter the meninges directly. The cerebrospinal fluid in these cases, instead of being a means of protection for the central nervous system, serves as a good medium for the dissemination of the bacteria.

Still another route for the entrance of bacteria into the cerebrospinal fluid is the ear. In advanced cases of otitis media or mastoiditis, the bacteria may enter the brain substance, in which case they produce a brain abscess with mere irritation or an inflammation of the meninges. They may also directly enter the meninges, in which case they produce a meningitis. This happens most frequently in infections with the pneumococcus, and with the hemolytic streptococcus.

Less frequently bacteria make their way into the cerebrospinal fluid through wounds of the skull and spine, especially through fractures of the skull.

Whichever way the bacteria enter the cerebrospinal fluid, once there, they produce changes in the meninges or brain and give rise to many alterations in the fluid. Some of the changes are common to all pathologic processes in the meninges or brain, whereas others are specific to certain bacteria or toxic substances.

PHYSICAL CHANGES

Color

In some pathological conditions the color of the fluid is altered while in others the fluid remains clear and colorless. In most acute suppurative meningitis the fluid is turbid.

In meningococcus meningitis the fluid has a yellowish green tinge. In pneumococcus meningitis the fluid is often pearly gray in color. In tuberculous meningitis and poliomyelitis the color of the fluid usually remains unchanged although occasionally the fluid is opaque, and at times yellow.

In hemorrhage of the brain the fluid is bright red when the hemorrhage is of recent origin and deep yellow when of long standing. Fluid contaminated with blood during spinal puncture is usually bright red in color and contains many erythrocytes.

A yellow fluid is also obtained in tumors of the cord and occasionally in chronic meningitis. The term xanthochromia has been used to indicate any yellow discoloration of the fluid. Xanthochromia and massive coagulation is a term used by Froin for a condition where the fluid is yellow in color and coagulates immediately after withdrawal from the body. This syndrome is present in tumors of the spinal cord.

In marked jaundice the cerebrospinal fluid often has the color of bile.

Increase in Amount of Fluid

It is the rule that whenever there is irritation in some serous cavity, the fluid normally present is increased in amount. This is true of the pleural cavity, the peritoneum, pericardium, and also of the meninges. Any irritation of the meninges, therefore, increases the amount of cerebrospinal fluid, the increase in some cases being only moderate, in others very great. Is every case of increased cerebrospinal fluid to be termed a serous meningitis as Quinke proposed? It would seem less confusing to use Dupré's term of meningism for all cases where the fluid shows only physical changes and reserve the term meningitis for all processes producing chemical, cytologic and bacteriologic changes. The name, however, makes little difference. It should be noted that the more acute the irritation, the

greater the amount of fluid accumulating in the ventricle and in the subarachnoid spaces.

There are, however, cases in which the fluid is decreased in amount. This occurs in tumors of the cord.

Pressure

With the increase in the amount of fluid in the subarachnoid space there is naturally an increase in the pressure of the fluid, so that we very seldom have a pathologic process of the meninges without a corresponding increase of the pressure of the fluid. Here also the character of the process and the degree of its acuteness determine the increase in pressure. Occasionally, however, there is a decrease in pressure. This is seen in tumors of the cord, where the communication between the ventricular and spinal fluid is blocked. This may also be found in brain tumors where there is a blocking of the foramen magnum by the tumor, and in obstructive hydrocephalus due to meningitis.

Foam

I found that all pathologic fluids produce a foam on shaking. When a test tube is filled one-third to one-half its depth with fluid, and is shaken for two or three minutes, a heavy foam one to two inches in thickness forms, persisting for half an hour or longer. When normal fluid is shaken in a test tube only a thin foam forms, disappearing in a few minutes. The foam is present in all pathologic fluids, but it is of greater size and duration in acute infections of the meninges. Recently Zingher described the formation of a heavy foam in poliomyelitis which corroborates my observations. It seems but natural to think that the foam production is due to the CO_2 in the fluid. Close observation, however, does not bear this out. I found repeatedly that a foam formed just as readily in fluid in which all the CO_2 had been driven off, if the fluid was pathologic. The foam, therefore, is best explained by the increased amount of protein in the fluid.

Pellicle

In addition to the physical changes which make their appearance in the cerebrospinal fluid under all pathologic conditions of the meninges, such as an increase in the amount, in the pressure, and the foam of the fluid, there is one change which takes place in the cerebrospinal fluid that is fairly characteristic for various diseases. This is the formation of a pellicle or sediment.

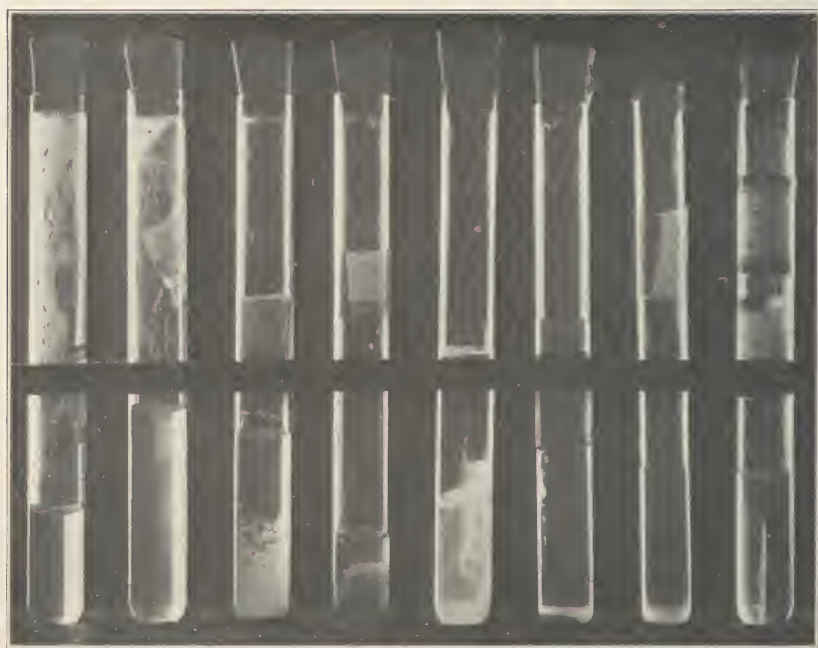


Fig. 31.—Photomicrograph of stained pellicle from cerebrospinal fluid of a pneumococcus meningitis.

In most acute diseases of the meninges a pellicle or a net of fibrin and blood cells forms in the fluid on standing. The time it takes a pellicle to form varies with the character of the disease. In suppurative meningitis, the pellicle forms in a very short time. In tuberculous meningitis, it takes from twelve to twenty-four hours for the pellicle to form, although I have seen it form in as short a time as one hour. Some authors have described a pellicle formation in poliomyelitis and in lues of the central nervous system. I have observed a pellicle in poliomyelitis only very rarely. I

have, however, observed a certain sediment in some cases of general paresis, tabes dorsalis and in certain cases of cerebrospinal lues. The sediment formed was flocculent in type, resembling the flocculi formed by the Noguchi test, or after the addition of sodium hydrate to the fluid of tuberculous meningitis.

The pellicle consists of a separation of the heavier ele-



A. B. C. D. E. F. G. H.

Fig. 32.—Pellicle formation in meningitis.

A. Normal. B. *Meningococcus meningitis*, fairly early. C. *Meningococcus meningitis*, advanced (sulphur-like granules). D. *Meningococcus meningitis*, late in disease. E. *Meningococcus meningitis*, severe, on road to recovery. F. *Pneumococcus meningitis*, fatal. G. *Pneumococcus meningitis*, fatal. H. *Tuberculous meningitis*.

ments of the cerebrospinal fluid, so that microscopically one can see in the pellicle many leucocytes on a fibrinous background. (Fig. 31.)

Fig. 32 illustrates the various forms of pellicle in various diseases as observed early before autolysis takes place.

Crystallization

Another physical phenomenon which takes place in cerebrospinal fluid on standing, is the formation of crystals, their character depending on the character of the disease.

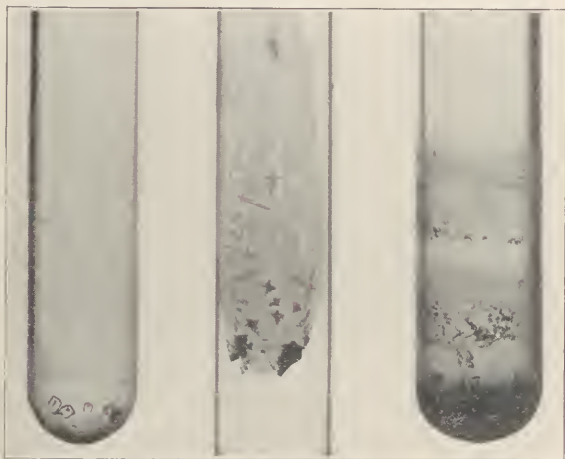


Fig. 33.—Crystals in test tube on spontaneous evaporation of cerebrospinal fluid from a case of tuberculous meningitis

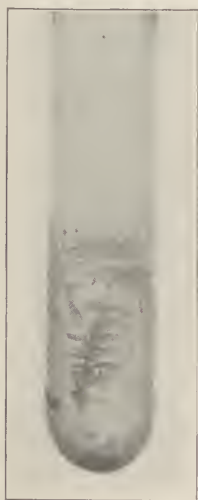


Fig. 34.—Spontaneously evaporated fluid from another case of tuberculous meningitis.



Fig. 35.—Spontaneously evaporated cerebrospinal fluid from a case of pneumococcus meningitis.

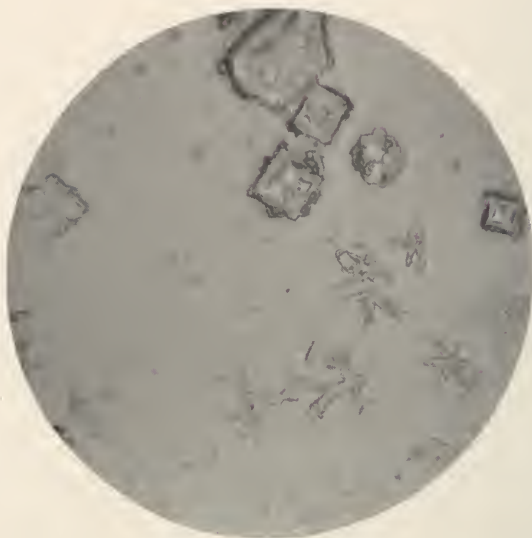


Fig. 36.—Crystals from an evaporated fluid in a case of tuberculous meningitis.
(76 diameters.)

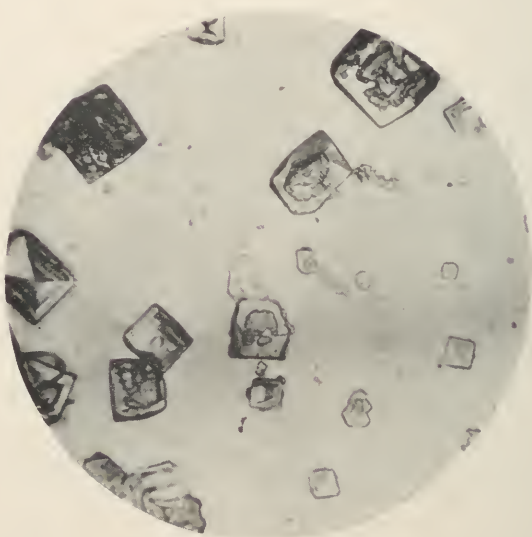


Fig. 37.—Crystals from another evaporated fluid of a case of tuberculous meningitis.
(76 diameters.)

Various authors have called attention to the crystals found in the cerebrospinal fluid. Mott speaks of cholin crystals in the fluid of patients suffering from disease producing a degeneration of the nervous tissue. Thomson describes the presence of elongated, colorless, transparent crystals in septic meningitis. He suggests that the acid radical present in the crystals is most likely phosphoric acid. I

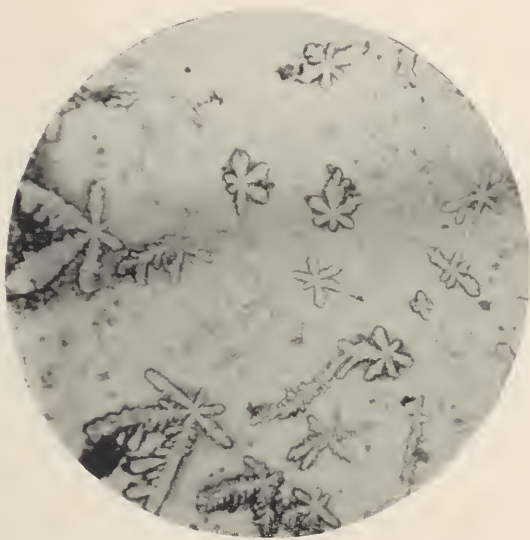


Fig. 38.—Crystals from an evaporated fluid of a case of pneumococcus meningitis.
(76 diameters.)

made a study of the crystalization process in a great number of pathologic fluids which were allowed to evaporate spontaneously at room temperature, and found that after several months of standing, most pathologic fluids showed the presence of many crystals of various sizes and shapes different from those formed in normal fluids. Figs. 33, 34 and 35 show the different forms of crystals present in different conditions, the varieties being even more distinct on microscopic examination. (Figs. 36, 37 and 38.)

CHEMICAL CHANGES

In all organic disturbances of the meninges, there are chemical changes of various degrees. The total nitrogen is usually increased. The organic index and the protein are also increased. The nonprotein nitrogen is increased only in certain diseases. Sugar and chlorides are increased in some diseases and decreased in others.

Permanganate or Organic Index

Mayerhofer was able to show by means of the Kubl Thiemich permanganate method that there is an increase in the organic substance in cerebrospinal fluid in all meningitides. This increase, he found, could be measured by the amount of permanganate necessary to oxidize the organic substance. Mayerhofer's observations led him to the following conclusions:

(1) That the reduction index of normal cerebrospinal fluid is low. Different portions of the same fluid give either the same reduction index or a different one, the tendency being toward a higher index in each subsequent portion.

(2) That the reduction index of meningitis is higher than that of normal cerebrospinal fluid (2 and up). Unlike normal fluid, the index becomes lower with each subsequent portion of the fluid.

(3) That the reduction index of cerebrospinal fluid in meningococcus meningitis drops to one-half its original pathologic rate after an injection of meningococcic serum.

My work on the permanganate index gave similar results. I found that fluid of all forms of meningitis gives a higher organic index than normal fluid and that the fluid of suppurative meningitides gives a higher organic index than fluid of tuberculous meningitis. Table XX gives some of the findings with the permanganate index in fluid of various diseases.

TABLE XX

ORGANIC INDEX IN CEREBROSPINAL FLUID IN VARIOUS FORMS OF MENINGITIS

NO.	DIAGNOSIS	PERMANGANATE INDEX				
		TUBE I	TUBE II	TUBE III	TUBE IV	TUBE V
1	Tuberculous meningitis	3.0		3.0		
2	Tuberculous meningitis	2.9	2.6	3.2		
	(Same case 4 days later.)	3.35			4.55 (15 c.c. between)	
3	Tuberculous meningitis	2.55	1.77	1.6		
	(Examined 2 days later)	2.95	1.55	1.75		
4	Tuberculous meningitis	3.1			2.7	2.7
	(Examined 3 days later)	3.9	1.8	3.0		
5	Tuberculous meningitis	2.1			1.8	
6	Tuberculous meningitis	2.6	2.2			
7	Meningococcus meningitis	7.9				
8	Meningococcus meningitis	5.6				
9	Meningococcus meningitis	2.0				
10	Meningococcus meningitis	9.2	9.3			
	(12 hours after serum injection)	7.3	8.7			
11	Influenza meningitis	2.6				
12	Pneumococcus meningitis	3.3	4.3	3.0		
	(Examined 7 days later)	4.6	4.3	4.6		
13	Pneumococcus meningitis	4.7		4.7	4.7	

Protein

In normal cerebrospinal fluid the protein content is small and consists mainly of globulin. In most pathologic conditions there is an increase in the amount of the protein, the increase usually varying with the severity of the disease. It has been found, however, that in some fatal cases of tuberculous meningitis, the fluid may contain a normal amount of protein. According to Mestrezat the serum

albumin is mostly increased in acute inflammatory conditions, and the globulin is increased in syphilitic affections of the cerebrospinal system as Table XXI of Mestrezat shows. (Figures expressed in grams per liter.)

TABLE XXI

	SERUM ALBUMIN	GLOBULIN	RATIO OF SERUM ALBUMIN TO GLOBULIN
Tuberculous	1.15	0.15	7/1
meningitis	1.35	0.25	5.5/1
	0.80	0.40	2/1
Cerebrospinal	1.80	0.30	6/1
meningitis	2.50	0.31	8/1
Syndrome of	4.90	1.30	3/1
massive coagulation	6.50	2.20	3/1

Hektoen and Neymann studied the action of specific anti-globulin and antialbumin precipitins on cerebrospinal fluid. They found that in the fluid of general paresis both albumin and globulin are increased, but principally the globulin, while in the fluid of epilepsy the increase of protein seemed to be in the albumin. Kirschenbaum and I found albumin in 2 cases of epilepsy. We also found albumin in the fluid of tuberculous and suppurative meningitis, and in syphilis of the central nervous system.

Precipitation

The action of precipitants on cerebrospinal fluid in various diseases furnishes further evidence of the varying character of the protein in different diseases. Tashiro and I found that in certain pathologic conditions a characteristic ratio may be obtained between the precipitate formed by sulphosalicylic acid and that formed by mercuric chloride. We based our comparison on the assumption that different processes respond differently to alkaloidal precipitants, such as sulphosalicylic acid and metallic precipitants, such as mercuric chloride (Tables XXII, XXIII, and XXIV, Fig. 39).

These findings speak in favor of my contention that there are specific changes produced by various disease processes which manifest themselves both chemically and physico-chemically. Although the fluid in cases of tuberculous men-



1. 2. 3. 4. 5. 6.

Fig. 39.—Photograph showing the typical ratio of precipitates by the two precipitants.

1. 1 c.c. of nonmeningitic fluid plus 1 c.c. of 3 per cent sulphosalicylic acid.
2. 1 c.c. of nonmeningitic fluid plus 1 c.c. of 1 per cent HgCl_2 .
3. 1 c.c. of fluid from tuberculous meningitis plus 1 c.c. of sulphosalicylic acid.
4. 1 c.c. of fluid from tuberculous meningitis plus 1 c.c. of HgCl_2 .
5. 1 c.c. of fluid from meningococcus meningitis plus 1 c.c. of sulphosalicylic acid.
6. 1 c.c. of fluid from meningococcus meningitis plus 1 c.c. of HgCl_2 .

ingitis contains less organic substances than the fluid of meningococcus meningitis as the table on organic index shows, still the mercuric chloride solution produces a heav-

TABLE XXII

COMPARISON OF AMOUNT OF SEDIMENT FROM THE METALLIC AND ALKALOIDAL
PRECIPITATION WITH NONMENINGITIC FLUIDS

NUMBER	DIAGNOSIS	MEASUREMENTS OF THE DEPTH OF SEDIMENT IN MM. AFTER 24 HOURS	
		HgCl ₂	Sulphosalicylic Acid
1	Psychosis	3	2
2	Tic	4	3
3	General paresis	4½	2
4	Delirium tremens	3	1
5	General paresis	3½	2
6	Psychosis	3	2
7	General paresis	3½	2
8	General paresis	3	0
9	Psychosis	4	3
10	Psychosis	4	0
11	Psychosis	4	2
12	Meningism	3	2
13	Dementia precox	3	0
14	Alcoholic	3	2
15	Psychosis	3	2
16	Psychosis	4	2
17	Psychosis	3	1
18	Psychosis	2½	2
19	Meningism	3	2

TABLE XXIII

AMOUNT OF SEDIMENT FROM THE METALLIC AND ALKALOIDAL PRECIPITATION
FROM FLUID OF TUBERCULOUS MENINGITIS

NUMBER	MEASUREMENTS OF THE DEPTH OF SEDIMENT IN MM. AFTER 24 HOURS	
	HgCl ₂	Sulphosalicylic Acid
1	10	4
2	15	4
3	10	3½
4	11	5
5	6	3
6	7	3
7	9	6
8	13	5
9	11	7
10	10	4
11	6	3
12	10	4
13	20	5

TABLE XXIV

MEASUREMENT OF SEDIMENT FROM METALLIC AND ALKALOIDAL PRECIPITATION
FROM FLUID IN MENINGOCOCCUS MENINGITIS BEFORE SERUM WAS GIVEN

MEASUREMENTS OF THE DEPTH OF SEDIMENT IN MM. AFTER 24 HOURS		
NUMBER	HgCl ₂	Sulphosalicylic Acid
1	1	8
2	2	7
3	1	20
4	1	10
5	7	20

ier sediment in tuberculous meningitis than it does in meningococcus meningitis. Table XXV shows further that the precipitants in question do not bear any quantitative relation to the amount of protein present in the cerebrospinal fluid.

TABLE XXV

CASE	DIAGNOSIS	APPEAR- ANCE OF FLUID	AMOUNT OF PROTEIN	MERCU- RIC CHLORIDE SEDI- MENT After 24 hours	SULPHO- SALICYL- IC ACID SEDI- MENT After 24 hours
230	Tuberculous meningitis	Clear	0.1%	20 mm.	5 mm.
231	Tuberculous meningitis	Clear	0.1%	18 mm.	7 mm.
232	Tuberculous meningitis	Clear	0.9%	14 mm.	6 mm.
233	Meningococcus meningitis	Turbid	0.3%	5 mm.	20 mm.
234	Meningococcus meningitis	Turbid	0.25%	7 mm.	20 mm.

Sugar

The study of sugar in the cerebrospinal fluid in its relation to certain diseases of the meninges, has occupied an important place in the literature. Kopetzky found an entire absence of sugar in all cases of meningitis. His method of determination, however, was only qualitative. Connall

reported an absence of sugar in all acute infections of the meninges. Schloss observed an absence of sugar in some cases of tuberculous meningitis and a small amount in others. Hopkins found a smaller amount of sugar in the fluid of syphilitics than in any other condition except meningitis. My own work on sugar in pathologic cerebrospinal

TABLE XXVI

SUGAR CONTENT IN THE CEREBROSPINAL FLUID OF LUES

NO.	WASSERMANN TEST	SUGAR CONTENT
1	Strongly positive	0.104%
2	Strongly positive	0.104
3	Positive	0.064
4	Strongly positive	0.048
5	Positive	0.070
6	Positive	0.074
7	Suspicious	0.080

TABLE XXVII

SUGAR CONTENT IN CEREBROSPINAL FLUID OF DIABETES

NO.	SUGAR CONTENT		
	Cerebrospinal Fluid	Blood	Urine
1	0.076	0.080	0.42
2	0.38		
3	0.28	0.24	

TABLE XXVIII

SUGAR CONTENT IN THE CEREBROSPINAL FLUID OF MENINGITIS

NO.	DIAGNOSIS	SUGAR
1	Tuberculous meningitis	0.08%
2	Tuberculous meningitis	Absent
3	Tuberculous meningitis	0.038
4	Tuberculous meningitis	0.032
5	Tuberculous meningitis	0.024
6	Tuberculous meningitis	Absent
7	Meningococcus meningitis	0.024
8	Meningococcus meningitis	0.028
9	Meningococcus meningitis	Absent
10	Meningococcus meningitis	Absent
11	Meningococcus meningitis	Absent
12	Pneumococcus meningitis	Absent
13	Pneumococcus meningitis	Absent

fluids with Strouse showed no alteration of sugar in the fluid of lues and gave an increase of sugar in diabetes. In meningitis it showed either an entire absence or small amounts or even normal amounts of sugar, depending on the type of organism causing the meningeal infection. Tables XXVI, XXVII and XXVIII give some of our results.

Cholesterol

Pighini found cholesterol in the cerebrospinal fluid of general paresis (88%), of epilepsy (66%), and of dementia precox (43%). Chaufford, Laroche and Grigant and Weston found small amounts of cholesterol even in normal fluid. Pighini determined cholesterol qualitatively by the Liebermann method, while Chaufford, Laroche and Grigant and Weston determined it quantitatively.

In a series of fluids examined by Landenberger, Howel and myself, no cholesterol or only very minute traces were found in normal fluids. The method used by us was that of Bloor with slight modifications.

Fluid in which the Wassermann and Lange reactions were positive also contained no cholesterol in appreciable amounts. Only three out of 25 such fluids gave a reading in the colorimeter.

Fluid from cases of hemorrhage of the brain showed high cholesterol content ranging from 8 to 17 mgm. of cholesterol per 100 c.c. of fluid.

Fluid from tumor of the brain gave a trace of cholesterol. Fluid from a case of brain abscess gave a high cholesterol reading, 13 mgm. per 100 c.c. of fluid.

The majority of meningitic fluids showed a trace of cholesterol. Three fluids had a high reading.

Ventricular fluid gave no cholesterol reading, except when there was the presence of hemorrhage of the brain or other pathological condition.

Urea, Phosphates, and Chlorides

Among the other chemical constituents that undergo changes in certain diseases, are urea, phosphates, cholin, lactic acid and acetone. In uremia the urea nitrogen has been found by me to be as high as 55 mg. per 100 c.c., compared to 20 mg. in normal fluid. Some workers have also observed an increase of urea in the fluid in cases of arteriosclerosis with symptoms pointing to an involvement of the central nervous system. Phosphates were found by Donath to be increased in conditions of rapid nerve degeneration, such as progressive paralysis, tabes dorsalis and tumor of the brain. Mott and Halliburton found cholin in the fluid and sometimes also in the blood in cases of severe nervous lesions, especially in paresis. Donath found cholin in the fluid of epileptics and paretics, the largest amount being present in the latter. Gumprecht found cholin in the fluid of chronic meningitis. According to Mott and Halliburton normal fluid contains no cholin, although Gumprecht found traces of it in normal fluid. Kauffmann and Stanford found no cholin in the fluid of general paresis.

The chlorides were increased in some cases of nephritis I examined. In the cases of meningitis I examined, the chlorides differed with the type of infection as seen from Table XXIX.

TABLE XXIX
CHLORIDES IN MENINGITIC FLUID

NO.	DIAGNOSIS	CHLORIDES IN GM.
		PER 100 C.C.
1.	<i>Streptococcus meningitis</i>	0.80
2.	<i>Meningococcus meningitis</i>	
	before serum	0.70
	Same patient after serum	0.72
3.	<i>Pneumococcus meningitis</i>	0.60
4.	<i>Tuberculous meningitis</i>	0.50

Lactic acid was increased in the cases of suppurative meningitis I examined. It usually took only 5 to 6 drops of

cerebrospinal fluid to turn 5 c.c. of Uffelmann's reagent to canary yellow instead of 18 to 20 drops required for non-meningitic fluid. Acetone was present in some cases after the fluid had been standing for several days. In a case of influenza meningitis there was a deep violet ring such as occurs in urine loaded with acetone. On a number of fluids from meningococcus meningitis the nitroprusside test for acetone gave a deep green ring.

Turbidity

By using one c.c. of cerebrospinal fluid in a test tube one-third inch in diameter, and adding small portions of decinormal sodium hydrate or decinormal sulphuric acid to the fluid, I was able not only to detect the presence of a pathologic process, but also to get a clue as to the type of the disease. Normal cerebrospinal fluid shows no turbidity on the addition of either sulphuric acid or of sodium hydrate. The fluid of tuberculous meningitis is not affected by sulphuric acid, but is precipitated by a very small amount of sodium hydrate. The fluid of suppurative meningitis, which is turbid to begin with, is cleared up by sodium hydrate and is not affected by sulphuric acid.

PHYSICOCHEMICAL CHANGES

Among the important changes that make their appearance in pathologic conditions of the nervous system are those of a physicochemical character. Although not all physicochemical changes are of diagnostic value, they are all of significance in that they bring out specific changes typical of special diseases. What is more, further investigations on the physicochemical changes taking place in pathologic cerebrospinal fluids give promise of an even wider range of information that can be applied with equal effectiveness to pathologic conditions of other body fluids, such as blood and urine.

Table XXX will show some of the variations found in

physicochemical constants in various pathologic conditions of the cerebrospinal fluid.

TABLE XXX
PHYSICOCHEMICAL FINDINGS IN VARIOUS FORMS OF MENINGITIS

	SPECIFIC GRAVITY	VISCOSITY	FREEZING POINT	CONDUCTIVITY	H-ION CONCENTRATION	ALKALINE RESERVE
Suppurative meningitis	1.0075	1.0434-1.0735	-55° to -57°C.	.011629	Immed. P_{H_2} 7.3 On Standing P_H Increases slowly or may become more acid	18- 38% of CO_2 bound by the fluid
Tuberculous meningitis	1.00693-1.00626	1.0693	-47°	.013660	7.4-7.6 Increases to 8.1 and higher	33- 58% of CO_2

A comparison of these figures with those given for normal fluid (Chapter IV) shows the great variation between the physicochemical constants of pathologic and normal fluids. Other authors have reported even greater differences. Achard, Loeper and Lanbry found the freezing point of fluid from tuberculous meningitis to be -44°, and that of meningococcus meningitis -46°, whereas the freezing point of normal fluid usually varies between -56° and -58°.

In addition to the meningitides, the fluids of diabetes and uremia show changes in the freezing point. The fluid in diabetes shows a freezing point of -.62 to -.69. The fluid in uremia has a freezing point of -.63 to -.73.

Protein Charges

It is well known that the electrical charge of a protein depends on the reaction of the medium. In acid solution,

proteins become electropositive, and in alkaline solutions they become electronegative, as shown in Table XXXI taken from Michaelis.

TABLE XXXI
SHOWING CATAPHORESIS OF PROTEINS

SUBSTANCES	H ⁺	MOVES TO
Casein.....	4.9×10^{-5} 4.1×10^{-5} 1.3×10^{-5}	Cathode Stand still Anode
Serum Albumin.....	$1.2 \times 10^{-4} - 2.1 \times 10^{-5}$ $2.0 \times 10^{-5} - 1.9 \times 10^{-5}$ $1.1 \times 10^{-5} - 1.9 \times 10^{-5}$	Cathode Stand still Anode
Oxyhemoglobin.....	2.4×10^{-7} 1.2×10^{-7}	Cathode Anode
Gelatin.....	1.5×10^{-5} $1.2 \times 10^{-5} - 3.5 \times 10^{-5}$ 3.9×10^{-5}	Anode Stand still Cathode

It is thus seen that one way of precipitating protein is to let it combine with some radicle to form an insoluble protein salt. From the standpoint of the electrical charge of the protein such a protein is necessarily either a positive protein radicle forming a protein salt with negatively charged ions (alkaloidal precipitants), such as tungstic, picric, tannic acid and the like, or a negatively charged protein combining with a positively charged metal (metallic precipitants) such as Cu, Ag, Hg, Zn, and Pb. If these protein salts are sufficiently insoluble, a precipitate will come down.

To ascertain whether the difference in the acidity of the cerebrospinal fluid under various conditions as discussed below is great enough to produce different electrical states of the proteins in the fluids, Tashiro and I have made a

series of observations. The apparatus used was the one recommended by Michaelis. (Fig. 40.)

The fluids were placed in 3, care being taken to see that there was no bubble inside the core of the stopcocks. Tubes 2 and 4 were filled with 3 per cent sulphosalicylic acid, and the upper portions (1 and 5), with distilled water. To one electrode was added CuCl_2 and to the other NaCl ; a silver electrode was put in the anode and a copper electrode in the cathode. The poles were connected to a light circuit

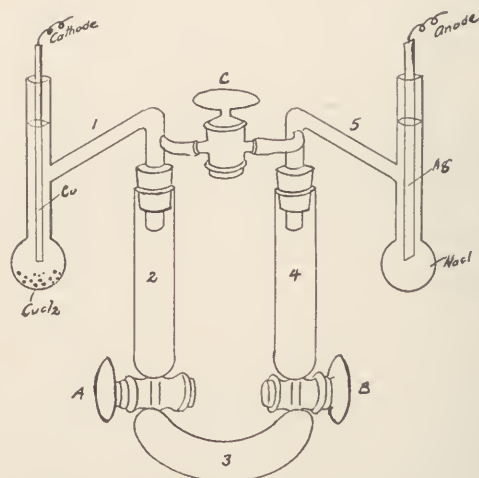


Fig. 40.—Apparatus for cataphoresis of proteins, after Michaelis.

with 110 volt constant current, with an ordinary lamp in the circuit as resistance. The object was to determine the pole to which the protein would move. The migration of the protein from the cerebrospinal fluid was detected by the formation of a precipitate with sulphosalicylic acid in the arm. This method, of course, is necessarily crude. For an accurate test it would be necessary that the H-ion concentration, the osmotic pressure of the precipitants and of cerebrospinal fluid be the same for each experiment—a procedure almost impossible on account of the variation in the fluid. Furthermore, under these conditions, positively

charged protein has a better chance of forming precipitates at the cathode, while negatively charged protein, which moves to the anode, must change its charge at the anode in order to combine with sulphosalicylic acid. In other words, the amount of negatively charged protein to be precipitated at the anode depends not only on the amount of protein that moves to the anode, but also on the strength of the acidity of the precipitating agent at the anode. Although this method is quite crude it is convenient for detecting the charge of protein in the cerebrospinal fluid.

TABLE XXXII

RESULTS OF CATAPHORESIS ON FLUID FROM CASES OF TUBERCULOUS MENINGITIS

NO.	TIME AFTER WITHDRAWAL	CATAPHORESIS	
		Cathode	Anode
1	2 hours	↓	↓
1	2 days	↓	↓
1	2 days	↓	↓
2	2 hours	↓	↓
2	3 hours	↓	↓
3	1 day	↓	↓
4	3 hours	↓	↓
5	24 hours	↓	↓

↓ Indicates heavy precipitate.

↓ Slight precipitate.

Tables XXXII and XXXIII show some of the results obtained on cerebrospinal fluid with the cataphoresis experiment.

As is seen from the tables, a considerable amount of the protein in meningococcus meningitis moves toward the cathode, showing the presence of positively charged protein in the cerebrospinal fluid of that disease. In tuber-

TABLE XXXIII

RESULTS OF CATAPHORESIS ON FLUIDS FROM MENINGOCOCCUS MENINGITIS

NO.	INTERVAL	CATAPHORESIS		REMARKS
		Cathode	Anode	
1	1 day	↓	↓	Fluid bloody Unusually alkaline fluid; cases not under author's care; administration of serum not ascertained.
1	1 day	↓	↓	
2	20 hours	↓	↓	
2	3 days	↓	↓	
3	3 days	↓	↓	
3	2 days	↓	↓	
3	3 hours	↓	↓	
4	8 hours	↓	↓	
5	3 hours	↓	↓	
6	↓	↓	
6	17 hours	↓	↓	
7	↓	↓	
7	2 days	↓	↓	

↓ Indicates heavy precipitate.

↓ Slight precipitate.

culous meningitis, however, the precipitate moves toward the anode, showing that the protein in that case is negatively charged. This again indicates the occurrence of specific biochemical changes in various diseases.

The Colloidal Gold Reaction

Lange has applied the work of Zsigmondy who found definite measures of the protective action of colloids on the precipitation of gold suspensions by sodium chloride, to the protein of cerebrospinal fluid. Lange found that nor-

mal cerebrospinal fluid when diluted with 0.4 per cent solution of sodium chloride does not affect the solution of colloidal gold, while pathologic fluid produces characteristic changes for various diseases. The exact mechanism of the gold chloride reaction is not well known, but we have here a distinct physicochemical reaction that not only signifies the existence of a pathologic state of affairs, but also indicates its nature as this test produces specific discolorations in various forms of the same disease, such as in the various types of neurosyphilis.

Mastic Reaction

Emanuel described a reaction obtained by adding a solution of mastic, the resin of *Pistacia lentiscus*, a tree of the *Terebinthaceae* to pathological cerebrospinal fluid. The mastic test seemingly works on the same principle as the Lange, and further corroborates the physicochemical specificity of disease.

Ninhydrin Reaction

Noble has applied the ninhydrin reaction of Abderhalden to the cerebrospinal fluid and found that in tuberculous meningitis a blue to a blue-violet color appears on boiling 0.5 to 1 c.c. of cerebrospinal fluid with 0.1 c.c. of 1 per cent ninhydrin solution for about one-half of a minute. Other workers have confirmed his observations.

Changes in the Reaction of the Cerebrospinal Fluid

Kopetzky applied the acidosis theory of Fischer to cerebrospinal fluid, claiming that the fluid presents an acidity of varying degree in all conditions which give rise to pressure symptoms of the brain. Kopetzky used litmus paper for his determination of the reaction and he also titrated the cerebrospinal fluid against decinormal sodium hydroxide solution. He expressed his results in grains of decinormal hydrochloric acid solution, estimated for 100 c.c.

of cerebrospinal fluid, using a one per cent phenolphthalein solution as an indicator.

I studied the reaction of cerebrospinal fluid in disease from various points of view using the titration, the H-ion concentration and the alkaline reserve methods for this purpose. Originally I determined the reaction of the cerebrospinal fluid by titrating the fluid against $n/100$ sulphuric acid. The following method was used:

In each of three Erlenmeyer flasks with a capacity of 50 c.c., 20 c.c. of distilled water was measured, all of the flasks being of the same height and width. Into each flask was put 1 drop of a 0.2 per cent solution of methyl red. This produced a straw-red color which was the neutral point. Then 1 c.c. of the fluid to be examined was placed in one of the flasks by means of a graduated pipette. This turned the solution still deeper yellow. The flask was now titrated with $n/100$ sulphuric acid until the neutral point was obtained. This was compared with the other two flasks, all three flasks being placed on a porcelain stand. When the neutral point was reached the reading was taken and then one more drop of the sulphuric acid was introduced. A bright red color appeared. In order to check the result 1 drop of $n/100$ NaOH was added. This gave the solution a straw color. Another drop was added which changed it to yellow, thus proving that the end point had not been overrun. This procedure gave no difficulty in obtaining a sharp end point.

With this method it was found that nonmeningitic fluid required between 1.5 and 2.6 c.c. $n/100$ sulphuric acid to reach the end point which would correspond to an alkaline reserve varying between 33 and 58 per cent total CO_2 . Fluid from meningococcus meningitis required between 0.7 and 1.3 c.c. of $n/100$ sulphuric acid which would correspond to an alkaline reserve varying between 18 and 29 per cent total CO_2 and fluid from pneumococcus meningitis, the same amount. Tuberculous meningitis, however, acted the same

TABLE XXXIV

TITRATION OF CEREBROSPINAL FLUID WITH METHYL RED AS INDICATOR

CASE	AGE	DIAGNOSIS	ACIDITY IN TERMS OF N/100 H ₂ SO ₄ WITH METHYL RED AS INDICATOR	OTHER TESTS	REMARKS
A—NONMENINGITIC					
1	11 yrs.	Epilepsy	2.2 c.c.	Negative	
2	12 yrs.	Typhoid	2.2	Negative	
3	8 yrs.	Encephalitis	2.4	Negative	
4	40 yrs	Lues	2.2	Wassermann Positive	
5	Adult	Cerebrospinal Lues	1.8	Wassermann Positive	
6	Adult	Insanity	1.9	Negative	
7	Adult	Insanity	2.0	Negative	
8	Adult	Nephritis	2.2	Negative	
9	11 mos.	Otitis media, pneumonia	1.5	Negative	
10	5½ mos.	Erysipelas	1.9	Negative	
B—MENINGITIC					
11	11 yrs.	Meningococcus meningitis Before serum	0.9 c.c.	Increased pressure. 41,200 cells, 100% polymorphonuclear. Meningococci in smear and culture.	After 3 doses of serum acidity 2.0 c.c.
12	10 yrs.	Meningococcus meningitis Before serum	0.9 c.c.	2,400 cells, 99% polymorphonuclear. Meningococci in smear and culture.	
13	4 yrs.	Meningococcus meningitis Before serum	0.7 c.c.	Several thousand cells per c.mm. 95% lymphocytes. Meningococci in direct smear and culture.	After serum 1.5 c.c.
14		Pneumococcus meningitis	0.9 c.c.	Chemical tests positive. Pneumococci in culture.	
15		Pneumococcus meningitis	1.1 c.c.	Pneumococci in culture.	
16	3 yrs	Tuberculous meningitis	1.9 c.c.	Tubercle bacilli found in fluid.	
17	20 mos.	Tuberculous meningitis	2 c.c. 2.1 c.c.	All chemical tests positive.	Autopsy proved diag- nosis.

as nonmeningitic fluid, requiring 1.5 to 2.6 c.c. of n/100 sulphuric acid to reach the end point. (Table XXXIV.)

After I had completed my investigation of the reaction of the cerebrospinal fluid by means of this titration method, it was realized that the fluid on which the work had been done had been standing too long before examination to give an accurate idea of the real acidity of the fluid. I was also aware of the fact that the titrable acidity does not represent the true hydrogen-ion concentration of the fluid although it does tell the titrable acidity or alkaline reserve. I, therefore, decided to determine whether there was a similar variation in the free hydrogen-ion concentration between the normal and meningitic fluids of special types. To make the test the gas-chain method of Michaelis was used, and, benefiting by the experience with nonmeningitic fluid, I

TABLE XXXV
H⁺ CONCENTRATION OF FLUID FROM TUBERCULOUS MENINGITIS

No.	PH										
	Imme- diate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days or Over
1	8.69(a)	8.98(a)	
2	7.9 (a)*	
3	7.9 (b)	
4	8.0 (b)	8.0 + (b)	8.6 (b)
5	8.6 (b)
6	7.4 (b)	
7	7.4 (b)	
8	7.4 (b)	
9	7.4 (b)	
10	7.4 (b)	8.0 (b)	8.0 + (b)	
11	7.6 (c)	8.2 (c)	
12	7.4 (b)	
13	8.2 (c)	
14	7.4 (c)	8.2 (c)	
15	8.0(c)*
16	8.1 (c)
17	8.0 (c)	
18	8.1 (c)	8.8 (a)	
19	7.4 (c)	8.1 (c)	
20	7.8 (c)*	
21	7.4 (c)	7.8 (c)	7.9 (c)	
22	8.1 (c)	
23	8.1 (c)	
24	7.7 (c)	8.4 (a)	
25	7.6 (c)	
26	7.4 (c)	7.6 (c)	7.6 (c)	7.8 (c)	7.8 (c)	8.1 (c)	
27	7.75(a)	8.5 (a)	
28	7.4 (c)	7.6 (c)	7.7 (c)	8.2 (c)	

* Corked

endeavored to examine fluid as soon after removal from the body as possible. To carry out the immediate examination it was often necessary to resort to the indicator method, using the Levy-Rowntree-Marriott standard and a special indicator, checking both indicators by the gas-chain apparatus. In over a hundred cases of meningitis examined and checked by the above methods, the following observations were made:

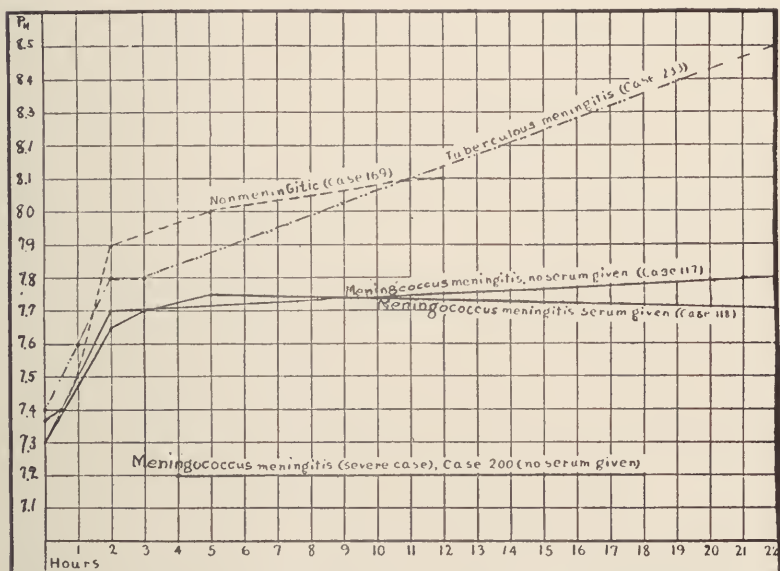


Fig. 41.—Change in the H⁺ concentration of three types of cerebrospinal fluid.

Fluid from cases of tuberculous meningitis differed in no respect from that of normal cases, the P_H being 7.4-7.6 immediately after withdrawal and ascending to 8.1 or higher. In some tuberculous fluids the H-ion concentration decreased in a much shorter time than in normal fluid (Table XXXV).

Fluid from cases of meningococcus meningitis showed an H-ion concentration slightly higher than that of normal, the P_H being 7.2 to 7.5 immediately after withdrawal, the average being 7.3. The greatest deviation from normal, however,

TABLE XXXVI

H+ CONCENTRATION OF FLUID OF MENINGOCOCCUS MENINGITIS BEFORE ADMINISTRATION OF SERUM

No.	PH										
	Imme- diate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days or Over
1	7.4 (b)
2	7.4 (b)
3	7.9 (b)
4	7.1 (c)	7.8 (c)
5	7.3 (c)	7.7 (c)	7.8 (c)
6	7.4 (c)
7	7.2 (c)
8	7.1 (c)
9	7.5 (c)
10	7.9 (c)
11	7.4 (c)
12	7.2 (c)	7.8 (c)
13	7.2 (c)	7.1 (a)
14	7.3 (c)
15	7.3 (c)	7.4 (c)	7.2 (c)
16	7.7 (c)	7.8 (c)
17	7.7 (c)
18	7.3 (c)	7.4 (c)	7.7 (a)	7.6 (c)	7.6 (c)	7.9 (c)
19	6.6 (c)
20	7.4—(c)	6.0 (a)
21	7.5
22	7.3—(c)	7.8 (c)
	7.4	7.8 (a)	7.8 (a)
	7.3 (c)	7.9 (c)

TABLE XXXVII

H+ CONCENTRATION OF FLUID OF MENINGOCOCCUS MENINGITIS AFTER ADMINISTRATION OF SERUM

No.	PH										
	Imme- diate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days or Over
1	7.4—(b)
2	7.4—(b)
3	7.4—(b)
4	7.0 (b)	7.4 (b)
5
6	7.4 (b)
7	7.0 (b)
8	7.1 (b)	7.4 (b)
9	7.1 (c)
10	7.4 (c)
11	7.3 (c)
12	7.7 (c)
13	7.6 (c)	7.8 (c)
14	7.2 (a)
15	7.1 (c)	7.9 (c)
16	8.1*
17	7.3 (c)	7.6—7 (c)	7.7— (c)	7.7—7.8 (c)	7.7 (c)
18	7.4	8.2

* Diagnosis was not settled.

was observed in fluid allowed to stand, the H-ion concentration then decreasing slowly in some cases, remaining stationary in others, and increasing in still others. Usually the graver the condition of the patient, the more turbid the fluid, and the longer the retention of the acidity. Administration of serum altered the H-ion concentration of the fluid, generally decreasing it. Cases of pneumococcus meningitis showed a strong resemblance to those of

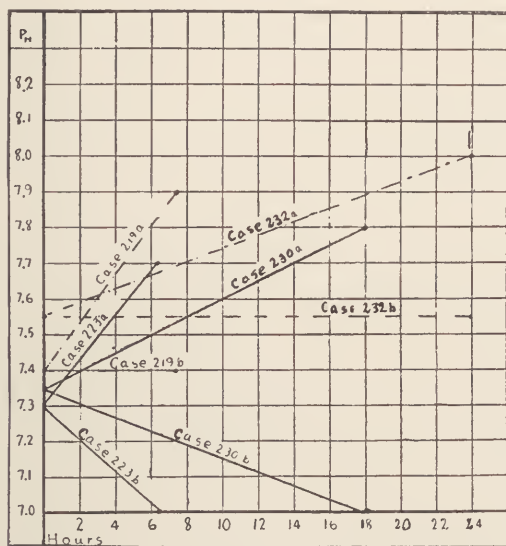


Fig. 42.—Different effects of corking on tuberculous and meningococcus fluids. Case 219a, tuberculous meningitis, cotton plugged; b, same fluid, tightly corked (no air above). Case 232a, tuberculous meningitis, cotton plugged; b, same fluid, corked (no air above). Case 223a, meningococcus meningitis, cotton plugged; b, same fluid, tightly corked (no air above); Case 230a, meningococcus meningitis, cotton plugged; b, same fluid, tightly corked (no air above).

meningococcus meningitis. (Tables XXXVI and XXXVII.) (Fig. 41.)

The slightly higher H-ion concentration of the fluid in suppurative meningitis as compared to normal, on immediate examination of the fluid, can be explained, I believe, by the bacterial fermentation of the dextrose in the fluid as indicated by the absence of sugar or the lessened amount of it in meningococcus meningitis—a fact

that has been brought out by several investigators. As for the mechanism responsible for the slow decrease in the H-ion concentration of fluid from suppurative meningitis, there are several possibilities to be considered, such as a slower loss of CO_2 in the fluid upon standing, a constant CO_2 production by the cells present in the sediment of the fluid, lactic acid formation due either to further fermentation of sugar by the bacteria in the test tube or to a destruction of the cells on standing of the fluid.

I found that the H-ion concentration of these fluids increased from 7.4 to 7.0 upon standing in tubes tightly corked, thus indicating that there is not only no loss of CO_2 , but that there is also a formation of certain acids on standing. Nonmeningitic and tuberculous fluids give quite different results (Tables XXXVIII and XXXIX). (Fig. 42.)

With the view of further ascertaining the cause of this increase of acidity the following experiments were made:

In one chamber of the biometer (Tashiro) was put 1 c.c. of tuberculous meningitis fluid, and exactly the same amount of meningococcus fluid in the other chamber. It was found that the tuberculous fluid gave off more CO_2 than the meningococcus, showing that although both tuberculous and meningococcus fluids give off CO_2 constantly, tuberculous fluid loses more CO_2 than does meningococcus. This suggests that the increased acidity in meningococcus meningitis is not due to a greater production of CO_2 but probably to the production of some other acid, very likely lactic acid.

Further work on the subject showed a greater amount of lactic acid in the fluid of meningococcus and other forms of suppurative meningitides than in that of normal or of tuberculous meningitis. Furthermore, upon standing, the fluid of suppurative meningitides showed an increase in its lactic acid content. This was more marked in the fluids that contained many polymorphonuclear leucocytes. Many fluids that showed no acetone immediately after with-

TABLE XXXVIII

TUBERCULOUS FLUID, CORKED

DATE DRAWN	DATE EXAMINED	INTERVAL	HOW STOPPERED	P _H
6/28/17 9:10				7.4
	6/28/17 3:05	5 hours	Cork	7.4
	6/28/17 3:05	5 hours	Cotton	7.9
7/13/17 11 a. m.	7/13/17 11 a. m.	Immediately		7.5-6
7/13/17 11 a. m.	7/14/17 11 a. m.	24 hours	Cork	7.5-6
7/13/17	7/14/17 11 a. m.	24 hours	Cotton	8.0

TABLE XXXIX

FLUID FROM MENINGOCOCCUS MENINGITIS, WITH CORK AND COTTON STOPPER

DATE DRAWN	DATE EXAMINED	INTERVAL	STOPPERED WITH	P _H
6/30/17 12:20 p.m.	6/30/17	Immediate		7.3
	12:20 p.m.			
	6:35 p.m.	6¼ hours	Paraffined cork	7.0
	6:35 p.m.	6¼ hours	Cotton plug	7.7
7/6/17 2:30 p.m.	7/6/17	Immediate		7.4
	2:30 p.m.			
	7/7/17	18 hours	Paraffined cork	7.3
	8:30 a.m.	18 hours	Cotton	8.2
7/11/17 11:30 a.m.	7/11/17	Immediate		7.4-7.5
	7/12/17	17 hours	Paraffined cork	7.4
	4:30 p.m.	17 hours	Cotton	8.1
7/11/17 1:30 p.m.	7/11/17	Immediate		7.3-7.4
	1:30 p.m.			
	7/12/17	18 hours	Paraffined cork	7.0
	7:30 a.m.	18 hours	Cotton	7.8
7/14/17	7/14/17	Immediate		7.3
	7/15/17	22 hours	Paraffined cork	7.1
		22 hours	Cotton	7.9

drawal, showed traces of it when allowed to stand for a day or two. These changes indicate that the increase, on standing, of the H-ion concentration of fluids from suppurative meningitides is due to a constant formation of organic acids, resulting from the decomposition of the cells in the fluid.

CYTOLOGICAL CHANGES

Cells

Any infection of the meninges gives rise to an increased number of cells in the cerebrospinal fluid. Often an irritation of the meninges will also cause an increase of cells in the fluid. During disease the cells differ as to their number and as to their origin according to the type and to the acuteness of the inflammation of the meninges. In order of their frequency the following types of cells are found in cerebrospinal fluid. (Fig. 43.)

1. *Small lymphocyte.* (Small mononuclear leucocyte.)

This type of cell which is present in small numbers (1 to 6) in normal fluid and which is present in large numbers in tuberculous meningitis, poliomyelitis and luetic infections of the meninges, is the size of a red cell and contains a deeply staining nucleus, which fills up nearly the whole cell. The small amount of remaining protoplasm takes the Wright, Unna Pappenheim or methyl blue stain less deeply than the nucleus and contains no granules.

2. *Large lymphocyte.* (Large mononuclear leucocyte.)

This cell which is occasionally present in normal fluid is present in large numbers in chronic inflammatory conditions of the meninges such as luetic affections of the meninges. The cell is twice the size of a red cell, and contains a round, less frequently oval nucleus which fills up the large part of the cell and which stains deeply by the ordinary stain.

3. *Polymorphonuclear leucocyte.*

This type of cell is found in great numbers in all septic processes of the meninges, in meningeal hemorrhage and at times also in brain abscess. The cell is one and a half to two times the size of a red blood cell. The nucleus is sub-

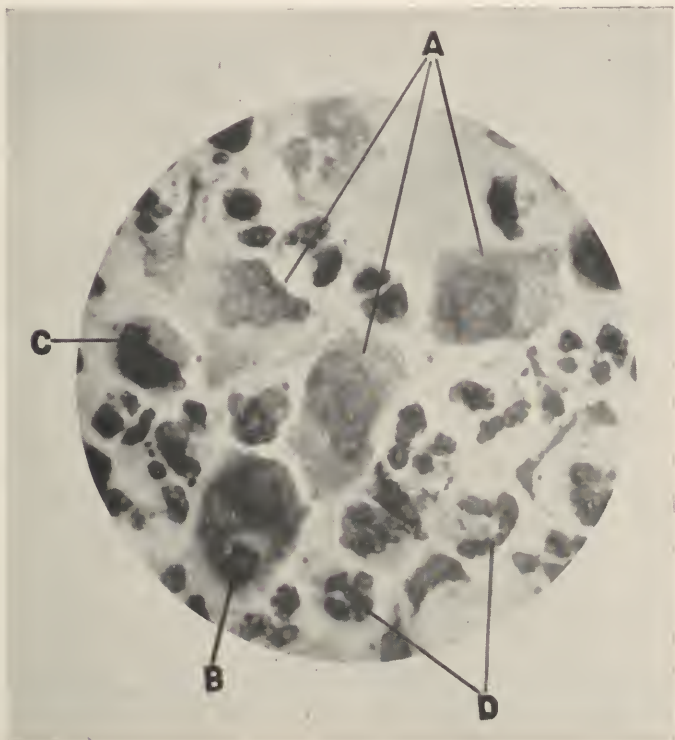


Fig. 43.—Photomicrograph showing types of cells in pathologic cerebrospinal fluid. $\times 1000$. *A*, endothelial cells. *B*, endothelial cell which has engulfed a polymorphonuclear leucocyte. *C*, large mononuclear cell. *D*, polymorphonuclear leucocytes.

divided into 2, 3 or 4 lobules and the protoplasm contains many granules, the granules being either small and neutrophilic in character or large and eosinophilic. Most of the polymorphonuclear leucocytes found in the cerebrospinal fluid are neutrophilic, eosinophilic leucocytes being found only seldom.

4. *Endothelial cell.* (Endothelial leucocyte, or transitional cell.)

This type of cell is supposed to be derived from the endothelial lining of the meninges. It is present in large numbers in the fluid of acute meningitis, especially in the fluid of meningococcus meningitis, and to a lesser degree in the fluid of subacute inflammatory processes of the meninges. Very seldom is an endothelial cell found in normal fluid.

The endothelial cell is larger in size than a large lymphocyte. It contains a small, round or oval, eccentrically placed nucleus, and a large amount of weakly staining protoplasm. The protoplasm often looks transparent and in places even seems to contain vacuoles.

Under the heading of endothelial leucocyte may be included the transitional cell, which is a large cell with indented or horseshoe-shaped nucleus. Many authors consider the transitional cell as an endothelial leucocyte.

The Gitterzell of the German authors is an endothelial cell in which the protoplasm is subdivided by fissures.

5. *Phagocyte.*

In meningococcus meningitis and less frequently in other meningitides, large cells containing smaller cells inside are seen in the fluid. The presence of phagocytes is not always an indication of the phagocytic action of the cells, and has no prognostic significance. The large phagocytes are probably the same cell as that listed under 4 above.

6. *Fibroblast.*

This cell which is derived from connective tissue is present in chronic inflammation of the meninges. The cell body is elongated, pointed at both ends and contains a small round or oval nucleus.

7. *Plasma cell.*

This cell which is found in old standing processes such as general paresis, is the size of a large lymphocyte or a little

larger. It contains coarse granules and a deep staining nucleus placed eccentrically.

8. *Erythrocyte.*

In fluid from meningeal hemorrhage, in all acute inflammatory processes and whenever blood has been obtained by an unsuccessful spinal puncture, red blood cells are found in the fluid.

9. *Tumor and cyst cells.*

Sarcomatous cells may appear in the fluid of a case of sarcoma of the meninges. Echinococci have been found in the fluid from cases of echinococcic cysts. Sicard reported a case where actinomycotic granules were found in the fluid.

10. *Unclassified cells.*

In all destructive processes of the meninges, cells are met in the cerebrospinal fluid in all stages of degeneration. The cells vary in size and shape and simply indicate destruction of the meninges.

Catalase

As pointed out above, normal cerebrospinal fluid contains no catalase or only a negligible quantity of the enzyme.

TABLE XL

CATALASE IN TUBERCULOUS MENINGITIS AND POLIOMYELITIS

DIAGNOSIS	INTERVAL	READING	CELLS PER C. MM.	OTHER TESTS
			AT TIME OF CATALASE DETERMINATION	
Tuberculous meningitis	5 hrs.	9, 11	800 cells, 80% lymphocytes	Tubercle bacilli in fluid
Poliomyelitis	7 days in ice box	6, 6	13 cells	Chemical tests positive
Tuberculous meningitis	5 days	0, 0	No cells now; 110 lymphocytes im- mediately after removal from body	Tubercle bacilli found in fluid; globulin posi- tive
Tuberculous meningitis	2½ days	3, 2	4 red cells, no white cells	Tubercle bacilli in fluid

Pathological fluid does contain catalase enzyme, the amount depending on the cells present or on the presence or absence of a pellicle.

TABLE XLI
CATALASE IN SUPPURATIVE MENINGITIS

DIAGNOSIS	INTERVAL	READING	CELLS AT TIME OF CATALASE DETERMINATION	OTHER TESTS
Meningococcus meningitis	½ hr.	14, 14	5,544 per c.mm. 90% polymorpho-nuclears	All bacteriologic and chemical tests positive
Meningococcus meningitis	4 days in ice box	6, 7	10 per c.mm.	All bacteriologic and chemical tests positive
Meningococcus meningitis after 90 c.e. serum	1 hr. at room temp.	20, 21	26 per c.mm.	Very high protein content; all other tests positive
Meningococcus meningitis	2 days	12, 12	All tests positive
Meningococcus meningitis after 30 c.e. serum	5 days in ice box	19, 18	All tests positive
Chronic basilar meningitis	4 hrs.	7, 7	100 per c.mm.	All tests positive
Meningococcus meningitis	19 days	6, 5, 6	All tests positive
Meningococcus meningitis before serum	4 days	4, 5	No white cells	All tests positive
Streptococcus meningitis	24 hrs.	20, 20, 38*	2,000	Streptococcus in direct smear in great numbers; all tests positive
Streptococcus meningitis	3½ hrs.	40, 35, 65*	960	Streptococcus in great numbers; all tests positive

*The pellicle was included in these tests.

BACTERIOLOGIC

Cerebrospinal fluid is sterile, even after it has passed through the nose as suggested by the cases of rhinorrhea reported in the literature. Any bacteria in the fluid, are, therefore, indicative of the existence of some pathologic

process in the body, unless it is known that the bacteria are the result of some external contamination of the fluid after having been removed from the body.

The cerebrospinal fluid is one of the best media for the growth of bacteria. However, at times it is very difficult to isolate bacteria from the fluid. Some bacteria, such as the pneumococcus and streptococcus grow easily on ordinary culture media; others, notably meningococci and influenza bacilli grow only on special media and at that with difficulty, while still others, like the tubercle bacilli can hardly be grown at all.

IMMUNOLOGIC

Immunology has thrown a great deal of light on the diagnosis and pathology of diseases related to the nervous system. The various agglutination tests help to differentiate the various types of meningococci. The hemolysin reaction indicates a permeability of the meninges, and the Wassermann test is an invaluable aid in the diagnosis of syphilis of the nervous system.

Agglutination

The agglutination test is based on the principle that various bacteria agglutinate when they are brought into contact with their respective sera. This principle is utilized for the identification of meningococci and pneumococci.

Inhibition of Saponin Hemolysis

Hauptmann found that normal cerebrospinal fluid has no inhibitory effect on the hemolysis of red cells produced by saponin, while certain pathological fluids, notably that of tumor of the brain, inhibit the saponin hemolysis of red blood cells. The following table shows Hauptmann's results:

Normal cerebrospinal fluid	No inhibition of hemolysis
Hemorrhage and softening of the brain of recent occurrence	85.7%
Hemorrhage and softening of the brain of long standing	No inhibition
Tabs	83% inhibition
Cerebrospinal lues	65% inhibition
Multiple sclerosis	46% inhibition
Epilepsy	No inhibition
Brain and cord tumor	100% inhibition

Hauptmann considers the inhibitory action of pathological cerebrospinal fluid to be due to the increased amount of cholesterol in the cerebrospinal fluid produced by the degeneration of nervous tissue. Our work corroborates his contention. The technic of the test will be described in the next chapter.

Hemolysin

Weil and Kafka demonstrated the presence of hemolysin or amboceptor and complement in the cerebrospinal fluid of certain affections of the central nervous system, especially where the meninges are involved. Normal cerebrospinal fluid, as pointed out in Chapter V, contains no hemolysin. Weil and Kafka explain the presence of hemolysin in pathological cerebrospinal fluid, by the increased permeability of the meninges, a condition present in all forms of meningitis, and according to them also in tabs and in general paresis. The authors consider the hemolysin reaction of great diagnostic and prognostic significance.

Wassermann Reaction

Various views have been expressed in the literature as to the principle underlying the Wassermann test; Pighini thought it due to cholesterol, others thought it due to the presence of protective antibodies in the blood or cerebrospinal fluid. My own work does not confirm the idea of

Pighini. It is also known that the Wassermann reaction is nonspecific, and is independent of true immunity. The usefulness of the test, whatever the underlying principles, is very great.

Most authors consider a positive Wassermann test of the cerebrospinal fluid to be specific for syphilis of the central nervous system. Positive tests are reported to have been found in the fluid of other conditions, such as leprosy and beriberi, still it is practically pathognomonic of lues, especially in harmony with the clinical condition and the history of the case. A negative Wassermann, however, does not always rule out syphilis.

Toxicity

The cerebrospinal fluid of many pathological conditions is toxic, notably the fluid of cases of tuberculous meningitis and epilepsy.

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CHAPTER VII

METHODS OF EXAMINATION OF CEREBROSPINAL FLUID FOR DIAGNOSTIC PURPOSES

In the following pages I shall outline the methods employed in the examination of cerebrospinal fluid for the purpose of detecting the presence of pathologic processes. I shall describe only those methods that have been proved to be both simple and practical for clinical purposes.

PHYSICAL

No special apparatus is required for the physical examination of the cerebrospinal fluid with the exception of that used for the determination of the pressure of the fluid (see description in Chapter III). All other physical examinations can be made by the naked eye. The amount of fluid withdrawn can be measured either in a graduate or it may be estimated. If the amount of fluid easily withdrawn from the patient in recumbent position exceeds 10 c.c., a pathologic condition should immediately be suspected and the fluid carefully examined.

Color

The best way to examine the fluid for color is to hold it up against the light with a background of black or yellow. The glass of the tube containing the fluid should be thin enough to show the color clearly and the tube itself should always be kept in the same position toward the light. Daylight naturally is better for the observation of color than artificial light. The specific changes of color in different conditions, in the various types of meningitis, and in conditions known as xanthochromia and in jaundice, are described under their respective headings.

Foam

If only five or ten c.c. of fluid is removed the tube containing the fluid should be shaken and watched for the formation of foam. The length of time the foam persists should be observed, and its character noted, as both furnish a clew as to the presence and intensity of pathologic processes.

If more than 10 c.c. is removed, the first tube, containing 2 to 3 c.c., should be put away for various examinations (Cf. Chapter III). The second tube, containing 3 to 5 c.c., should be left undisturbed for film or pellicle formation. The third tube, containing preferably between 9 and 10 c.c., although 5 c.c. will also do, should be tested for foam formation. After the foam has subsided, the fluid in this tube may be used for any purpose desired.

Film or Pellicle

In looking for a film or pellicle, one must be careful not to disturb the fluid. It is therefore best to put the tube aside for this purpose, as soon as the fluid is collected. As for the best conditions under which a pellicle will form, no set rules can be given. Generally, a pellicle will form either at room temperature or in the cold. My experience has shown that a pellicle forms more easily at room temperature than on ice. Hence, the tube in which the pellicle is expected to form should be left at room temperature, absolutely undisturbed. Another point is that the pellicle must be examined not later than twenty-four hours after the withdrawal of the fluid, as autolysis often takes place in the pellicle on standing for two or three days.

CHEMICAL

Many qualitative and quantitative chemical tests have been used by various scientific workers. Not all of the tests, however, are necessary or applicable for routine diagnostic purposes.

The chemical examinations of the cerebrospinal fluid for diagnostic purposes may therefore be limited to globulin tests, permanganate index, sugar, urea and chlorides. In a rapid examination of the fluid all but the globulin test may be dispensed with as the globulin increase is the one chemical factor common to all inflammatory processes, whereas the sugar and chloride content often remain unchanged. In making the chemical tests one should make sure that all the vessels employed are chemically clean.

GLOBULIN TESTS

Several globulin tests have been proposed. Among the most important of them are the Noguchi, Ross-Jones, Nonne-Apelt, the Pandy, and the sulphosalicylic mercuric chloride tests. In doing any globulin test one must make sure at the beginning that the fluid is perfectly free of blood. Should there be any blood present in the fluid the globulin test will be positive even if no pathologic process exists. The effect of centrifugation on the fluid is not marked. I found very little difference between the globulin reaction of centrifuged and uncentrifuged specimens. The cells present in the fluid neither interfered with nor accelerated the positiveness of the globulin test. A description of the various globulin tests follows:

Ross-Jones

The Ross-Jones test consists of the superimposition of 0.1 c.c. to 0.3 c.c. of a saturated solution of ammonium sulphate upon an equal amount of cerebrospinal fluid. If the globulins in the fluid are increased, an opaque ring develops at the point of contact of the fluid and ammonium sulphate. The ammonium sulphate solution is prepared in the following manner: 85 grams of ammonium sulphate is put into 100 c.c. of water and boiled in an Erlenmeyer flask until no more salt goes into solution. This is then

filtered and used for the test. The ammonium sulphate solution should be neutral in reaction, for if it has an acid reaction the results will not be accurate.

Nonne-Apelt

Phase I.—The constituents used for the Nonne-Apelt test are the same as those used for the Ross-Jones, except that equal parts of the cerebrospinal fluid and saturated ammonium sulphate are mixed instead of being superimposed one upon the other. A white precipitation forms in three minutes if the reaction is positive (euglobulin).

Phase II.—The precipitate is filtered, one drop of 10 per cent acetic acid is now added to the filtrate and the mixture is boiled. A precipitate forms if the reaction is positive (serum albumin).

Pandy

One drop of cerebrospinal fluid is added to one c.c. of a concentrated solution of carbolic acid (1 part of phenol crystals to 16 parts of water). A cloudy streak descending in the carbolic solution is noticed if an excess of globulin is present.

Noguchi

Two-tenths c.c. of cerebrospinal fluid is transferred by means of a pipette to a small test tube, preferably a regular Noguchi tube. Five-tenths c.c. of butyric acid solution (5 c.c. of butyric acid to 45 c.c. of physiologic salt solution) is added to the fluid; this mixture is boiled for a few seconds and 0.1 c.c. of a 4 per cent aqueous NaOH solution is poured into it and it is boiled again for a few seconds. If there is an increase in the globulin of the fluid a fine or coarse granular, flocculent deposit is formed in from two to twenty minutes. If no flocculence makes its appearance within two hours, or if nothing more than a slight opalescence is present, it shows that the globulin is not increased.

Recently Noguchi described a new test for the detection of increased protein in the cerebrospinal fluid. The reagent for the test consists of an alcoholic extract of acetone-insoluble tissue lipoids and a solution containing 0.5 c.c. of glacial acetic acid, 10 c.c. of a saturated solution of picric acid in absolute alcohol, 1.5 gm. of acid potassium phosphate and 4 gm. of sodium chlorid in distilled water to make the total volume 1,000 c.c. One c.c. of the reagent added to 0.1 c.c. of cerebrospinal fluid shows a flocculent precipitate if the protein in the fluid is increased.

Noguchi claims great accuracy for this test. However, the necessity of preparing a stock solution of acetone-insoluble lipoids, will, I believe, hinder the test from becoming popular in clinical laboratory work.

Kaplan

Five-tenths c.c. of cerebrospinal fluid is heated and boiled twice. Then 3 drops of a 5 per cent solution of butyric acid in physiologic salt solution is added to the test tube and is followed immediately by 0.5 c.c. of a supersaturated solution of ammonium sulphate. The mixture is now set aside for 20 minutes. An excess of globulin is indicated by a thick granular precipitate.

Sulphosalicylic Mercuric Chloride Method

One c.c. of cerebrospinal fluid is introduced into each of two small tubes of uniform height and width, (about 0.3 cm. in diameter); into one of the tubes 1 c.c. of a 3 per cent sulphosalicylic acid is introduced, and into the other 1 c.c. of a 1 per cent mercuric chloride. If the fluid is pathologic, a heavy precipitate forms in the tube containing the sulphosalicylic acid; if the fluid is normal only a slight turbidity appears. The tubes are then allowed to stand for twenty-four hours, after which the sediment in them is measured and compared. Under normal conditions the sediment found after 24 hours in either of the two tubes is very

slight; in all suppurative meningitides, however, the precipitation with the sulphosalicylic is very heavy, often being three times the size of the precipitation obtained with the mercuric chloride. In tuberculous meningitis (and occasionally also in general paralysis) the opposite takes place, the precipitation with the mercuric chloride usually being three times as heavy as that obtained with sulphosalicylic acid.

Relative Value of the Globulin Tests

It would be well to emphasize the fact that there is no one test for the diagnosis of pathologic conditions that can be considered absolutely final. Furthermore, even all the tests together are at times unreliable, unless supported by additional observations. A careful worker soon learns that to make a correct diagnosis he must take into account the entire picture of the disease gained from both clinical and laboratory observations. There are so many possibilities for error in laboratory work that unless one combines the clinical with the laboratory results, he is apt to arrive at erroneous conclusions. As for the relative value of the different tests, the experience of different workers varies. As a rule the Ross-Jones, Noguchi and Pandy run parallel in the same case. The Ross-Jones and Pandy have the advantage of being odorless and requiring no boiling. I also found the sulphosalicylic mercuric chloride test very helpful in the diagnosis of tuberculous meningitis. Early in the course of the disease when other tests could not be depended on for definite results this test often gave a positive reaction. Many of my colleagues report a similar experience with this test.

The Permanganate Test

One c.c. of cerebrospinal fluid is introduced into an Erlenmeyer flask by an accurately graduated pipette; 50 c.c. of distilled water and 10 c.c. of diluted sulphuric acid (one part H_2SO_4 and three parts H_2O) are added, and the mixture

is brought to the boiling point; 10 c.c. of a decinormal permanganate solution is then introduced into the flask and the solution is boiled for exactly ten minutes. At the end of this time 10 c.c. of decinormal oxalic acid is put into the flask, whereupon the red or yellowish-red color turns white. Titration is now carried on drop by drop from a burette containing the permanganate solution until the color of the solution in the receptacle turns red and remains so for a number of minutes. The number of cubic centimeters of permanganate required to produce the end reaction is then read off and the figure is taken as the permanganate index. In doing this, one must make certain that 10 c.c. of $n/10$ permanganate equals 10 c.c. of $n/10$ oxalic acid. It is also necessary to ascertain how much permanganate is required to oxidize the water and the H_2SO_4 and this amount should be subtracted from the number of cubic centimeters of permanganate required to oxidize the cerebrospinal fluid solution. For example, if 4 c.c. of $n/10$ permanganate was required for the cerebrospinal fluid and 0.5 c.c. permanganate for water and H_2SO_4 , the 0.5 c.c. should be subtracted from the whole number, leaving the reduction index only 3.5.

Boveri simplified the permanganate test. He uses 1 c.c. of cerebrospinal fluid and 1 c.c. of a 1 per cent permanganate solution. If the cerebrospinal fluid is normal, there is no change of color on contact of the fluid with the permanganate. In all pathologic fluids, a yellow ring forms on contact. When the fluid and the permanganate solution come into contact, the change in color appears in a few seconds or at most in a few minutes. The quicker the reaction, the more pathologic the fluid.

Sugar

The qualitative determination of sugar in the cerebrospinal fluid may be done by Fehling's solution. When there is no reduction of the Fehling's solution by the cerebrospinal fluid, suppurative meningitis should be considered,

as in most suppurative meningitides the sugar is absent from the fluid or greatly reduced in amount. For a more accurate determination of a reduction in the amount of the sugar in the fluid, quantitative methods should be employed.

Several methods have been employed for sugar determination, the most accurate ones being the Lewis-Benedict and the Folin-Wu methods, originally described for blood sugar. The technic of the Lewis-Benedict method is as follows: 2 c.c. of cerebrospinal fluid is put into a 25 c.c. volumetric flask containing 5 c.c. of distilled water, 15 c.c. of saturated picric acid solution is added, water filled up to 25 c.c. and the whole solution is shaken and filtered. Eight c.c. of the filtrate in duplicate are put into large Jena test tubes for determination; 2 c.c. saturated picric acid solution and 1 c.c. of a 10 per cent sodium carbonate solution are added; the contents of the tube is evaporated over the flame until precipitation occurs, 3 c.c. of water is added and the tube heated again to the boiling point, in order to dissolve the precipitate; the content of the tube is now transferred to a 10 c.c. volumetric flask, cooled, filled up to the mark with water, shaken and filtered through cotton into a colorimetric flask; the color is compared in a Duboseq colorimeter either with a dextrose standard, freshly made up every time, or with a permanent standard consisting of 0.064-mg. picramic acid and 0.1 gm. sodium carbonate in 1000 c.c., and the results are calculated.

Epstein described a rapid microchemical method for the determination of sugar in the blood which I believe may easily be applied also to the cerebrospinal fluid. The principle is the same as that of the Lewis-Benedict method, except that a permanent standard is used and smaller quantities of the fluid to be tested are used. It differs from the blood sugar test also in that in the determination of sugar in the cerebrospinal fluid, no sodium fluoride or potassium oxalate has to be used as is the case in sugar of the blood. The apparatus consists of the following:

(a) A Sahli-Gower hemoglobinometer stand and a graduated tube.

(b) Two standard color tubes, one for measuring quantities of sugar ranging from 0.05 to 0.1 per cent and the other for measuring quantities of sugar over 0.1 per cent.

(c) A test tube ($\frac{1}{2}$ by 4 inches) graduated at 1.0 c.c. and 2.5 c.c.

(d) A special pipette graduated at 0.1 c.c. and 0.2 c.c. (As will be seen later, this pipette may be dispensed with.)

(e) A test tube suitable for boiling fluid.

The procedure is as follows: 0.2 c.c. of cerebrospinal fluid is drawn up with the pipette of the apparatus or any other graduated pipette into the large graduated test tube. Distilled water is then drawn up into the pipette and discharged into the graduated test tube, till the fluid reaches the 1.0 c.c. mark; picric acid is added to the 2.5 c.c. mark, and the tube shaken vigorously; the contents are filtered through a small filter, or centrifuged for 2 to 3 minutes; 1 c.c. of the filtrate is now withdrawn, put into the boiling tube and heated carefully over the naked flame. The contents of the tube is boiled until all but 2 or 3 drops of the solution is evaporated. Five-tenths c.c. of a 10 per cent soda solution is now added and the tube heated again until the contents are down to a few drops, the color of the fluid being changed from yellow to deep red or reddish brown. Three or four drops of distilled water are added and the tube warmed gently. The contents are next transferred to graduated tube 1. The boiling tube is rinsed several times with a few drops of water, the tube being warmed with each rinsing. The volume of the fluid is then made up to mark 50 on the scale. The color of the resulting solution is now compared with one of the two standard tubes, A or B. If the fluid tested is darker than the standard A which represents 0.05 per cent of sugar, and is lighter than standard B which represents 0.1 per cent of sugar, the first standard is used for comparison. The solution in the

graduated tube is gradually diluted with water until the color matches. The percentage of sugar on using standard A is figured out, each reading on scale being 1/1000. For example, if the reading is 86 then $86/1000 = 0.086$ per cent. If B is used, the figure on the scale is multiplied by 2 divided by 1000. For example, if the reading is 73, then

$$\frac{73 \times 2}{1000} = 0.146.$$

I have checked the Epstein method against the Duboseq colorimeter with a standard solution of dextrose. The determination by Epstein method usually gave a higher reading of dextrose than the amount originally started with. The percentage of error, however, was small. I think it could be accounted for by the fact that the picramic acid used by Epstein in the standard tubes loses some of its potency in time; the result being that the solutions to be tested gave a higher percentage of sugar than the solution really contained. I have also encountered difficulty in using the pipette designated by Epstein for drawing up the fluid. The lumen of the pipette was too large so that when I succeeded in getting 0.2 c.c. of cerebrospinal fluid, the fluid would run out of the tube before I had a chance to empty it into the test tube. This difficulty, however, was done away with by calibrating my own tubes, using graduated pipettes and ordinary centrifuge tubes for that purpose, so that I had a double check on the amount used. I let the cerebrospinal fluid drop down into the centrifuge tube up to the 0.2 c.c. mark on the tube, using the same tube for the purpose of centrifugation.

Chlorides

For the quantitative estimation of chlorides in the cerebrospinal fluid, the Seelman method originally described for the determination of chloride in urine is the most practical. It requires only 0.5 c.c. of fluid and the results are quite accurate.

Two solutions are prepared for the test. Solution 1 consists of the following:

Anhydrous, crystallized silver nitrate, (C. P.).....	29.055	gm.
25% nitric acid in distilled water.....	900.	c.c.
Cold saturated solution of ammonioferrie alum in distilled water	50.	"
Distilled water, q. s.....	1000.	"

Solution 2 consists of:

Ammonium sulphocyanate	7	gm.
Distilled water	1000	c.c.

Solution 2 is intentionally made too strong, and must be standardized by adding distilled water in such an amount that exactly the last drop of 2 c.c. of this solution will bring about the end reaction when added to 1 c.c. of Solution 1. The end reaction consists of a reddish-brown color, which does not disappear on moderate stirring. If the second last drop produces a discoloration which disappears rather slowly, and the last drop a deep brown color, the solution must be still further diluted, until the discoloration on the addition of the last drop is a light reddish-brown, which does not disappear on stirring fifteen to twenty seconds.

The test proper is made as follows: 0.5 c.c. of cerebrospinal fluid to be tested is placed in a porcelain dish, 1 c.c. of Solution 1 is then added and the mixture is stirred for about a minute with a glass rod. Solution 2 is now added drop by drop by means of a 2 c.c. pipette graduated to at least 0.05 c.c. and the mixture is stirred until the brown color developing after each drop disappears. The amount of Solution 2 which has been used to bring about the end reaction is now read off, and the difference between this and 2 is equal to the number of grams of sodium chloride per 100 c.c. of the specimen tested. If for example, it takes 1.26 c.c. of Solution 2 to bring about the end reaction, the amount of chloride in 100 c.c. of cerebrospinal fluid equals $2 - 1.26$ which equals 0.74 per cent of chlorides.

PHYSICOCHEMICAL METHODS

If determined accurately, specific gravity, viscosity, surface tension and freezing point, are of some value in elucidating diagnosis of pathologic conditions. However, since accurate determinations of physicochemical constants require a great deal of care and consume a good deal of time, I do not recommend most of them for routine laboratory use. I believe, for instance, that specific gravity, to be of any value, should be determined by a pyknometer, the determination of specific gravity by the urinometer method being very inaccurate, and requiring more fluid than can be spared even in pathologic conditions. The pyknometer, however, is a delicate instrument, and consumes a great deal of time in drawing up the fluid without bubbles, in weighing the instrument, and also in keeping it at a constant temperature. It is, therefore, best to leave it out in ordinary laboratory work.

The determination of the H-ion concentration and of the alkaline reserve of cerebrospinal fluid, however, is of greater value than some of the other physicochemical constants. As has been shown in Chapter V the H-ion concentration and the alkaline reserve varies in the different types of meningitis especially after the fluid stands uncorked. This makes it of some diagnostic importance. I would, therefore, advise to determine the H-ion concentration and the alkaline reserve whenever a sufficient amount of cerebrospinal fluid can be spared after other more important tests have been made. The method for the H-ion concentration in routine laboratory work, I would recommend, is that of Levy-Rowntree-Marriott. This method requires only 3 c.c. of cerebrospinal fluid and very little apparatus. The gas-chain method, although more exact, requires 7 to 8 c.c. of fluid and is highly complicated. The technic of the Levy-Rowntree-Marriott method is as follows:

Three c.c. of cerebrospinal fluid is collected directly from

the lumbar puncture needle, or from another test tube into a nonsol glass tube. To this is added 0.2 c.c. of the indicator which consists of a solution of 0.01 per cent of phenolsulphonaphthalein. The tube with the cerebrospinal fluid is now compared in a special stand with one of the series of sealed standards ranging from a P_H of 6.6 to a P_H of 8.6.

If sufficient fluid has been obtained, it is advisable to determine the H-ion concentration immediately after the fluid has been removed from the body and also several hours later. If no large amount of fluid can be spared, the H-ion concentration should be determined only once, immediately after the removal of the fluid from the body. It must always be kept in mind that the H-ion concentration changes on standing and the time factor must be taken into consideration in order to arrive at any conclusion.

Some authors have used a dialyzing tube for the determination of the H-ion concentration of the cerebrospinal fluid by the indicator method. I have, however, found that with the exception of severe cases of suppurative meningitis where the protein content is very high, no dialysis is necessary and that the result obtained by the indicator method corresponds quite well with those obtained from the gas-chain method, especially in P_H readings of 7.0 to 8.1.

For the determination of the alkali reserve, the Van Slyke method is the most accurate and requires the least amount of fluid.

Lange Gold Chloride Test

The Lange test is very sensitive and is quite helpful in detecting various forms of syphilis of the nervous system and often also in differentiating the type of meningitis. The test, however, calls for extraordinary care and precision on the part of the one who is making it. To begin with, the vessels in which the solutions are used must be perfectly clean. Secondly, the vessels must be neutral in

reaction. Thus, after the glassware has been cleaned with bichromate solution, for instance, sufficient water should be run through the vessels to make the reaction neutral. The water used in making up this solution should be doubly distilled, and if possible, trebly distilled. It is preferable to use the formaldehyde from a one-pound container than from the usual fifty-pound carboy, as the formaldehyde in the smaller receptacle does not deteriorate so rapidly nor increase its acidity so greatly. The pipettes used for measuring the cerebrospinal fluid and sodium chloride solution must be accurately graduated. Great care must also be taken not to blow the pipette in emptying the solution, for the introduction of saliva or carbon dioxide into the solution will greatly interfere with this delicate physicochemical reaction. There is one point, however, in which the Lange test requires less precaution than other tests and that is in the matter of the time intervening between the drawing of the cerebrospinal fluid and the application of the test. While in an examination for pellicle or for the cells of the cerebrospinal fluid time of standing is a great factor, the examination with colloidal gold may be made, even after the cerebrospinal fluid has been standing for some time.

Preparation of Reagent

The solution for the test is prepared in the following manner:

To 1000 c.c. of doubly distilled water, which is heated slowly to 60° C., 10 c.c. of a 1 per cent gold chloride solution and 7 c.c. of a 2 per cent solution of potassium carbonate (K_2CO_3) are added. The mixture is then rapidly heated to 90° C. The flame is then removed and 5 c.c. of a 1 per cent formaldehyde solution is added quickly. The solution should at once assume a ruby red color. The solution when ready for use should be transparent, should be neutral in reaction, and should be precipitated by 1.7 c.c. of a 1 per cent sodium chloride solution in one hour. The solution

usually remains indefinitely without spoiling, although it is best to keep it in a bottle wrapped in dark paper.

Several modifications of the above technic have been proposed. The most recent modification is that of Lederer, who claims that his technic always gives practically uniform solutions conforming to accepted standards. His procedure is as follows:

Five hundred c.c. of distilled water is poured into a liter Erlenmeyer flask. Five c.c. of a 1 per cent solution of gold chloride, 3.5 c.c. of 2 per cent potassium carbonate solution, 0.87 c.c. of 1 per cent oxalic acid solution and 0.2 c.c. of a 2.5 per cent solution of formalin, are added to the water. The flask is placed over a flame, the base of the flask being protected with a square of asbestos, and the solution is heated gently until swirls of water begin to rise to the surface. The flame is adjusted so that the temperature of the solution remains at this point for about 40 to 45 minutes, precaution being taken not to permit bubbling to occur. At the end of this period the solution should become dark.

When this is noted, more formalin is added drop by drop, the fluid meanwhile being gently agitated by a rotatory movement of the flask. Soon a brownish-red discoloration appears following the formalin drop. The solution becomes darker and darker, changing to a reddish color, and suddenly it takes on the typical old rose hue. The flask is then removed from the flame and allowed to cool.

The amount of formalin to be used varies from about 1.7 to 2.2 c.c. In preparing several batches of solution at the same time, each one may require a different amount, the author states.

Examination of the Cerebrospinal Fluid

The technic of examining cerebrospinal fluid for the colloidal gold test is as follows:

A series of 10 large test tubes are put in a test tube rack and numbered. In the first test tube 0.2 c.c. of cerebro-

spinal fluid is poured and to it is added 1.8 c.c. of a 0.4 per cent solution of sodium chloride. Into each of the other tubes, 1 c.c. of sodium chloride is poured. The contents of the first tube are then thoroughly mixed and 1 c.c. of the amount is poured into the second tube. The contents of the second tube are then mixed and 1 c.c. of its solution is emptied into the third tube; and so the processes continue with all the tubes, until 1 c.c. of the solution in the ninth tube has been emptied into the tenth tube. The solution in the tenth tube is then thoroughly mixed and 1 c.c. of its contents is removed and discarded. This leaves each tube with a content of 1 c.c. and gives the following series of dilution 1:10, 1:20, 1:40, 1:80, 1:160, 1:320, 1:640; 1:1280; 1:2560, 1:5120. Five c.c. of the prepared colloidal gold solution is then added to each test tube and the tubes are put away and the changes taking place in them observed. Generally some change occurs in a very short time, but it is best not to attempt to judge the reaction before the lapse of an hour and it is still better to wait until the next day, for sometimes it takes 24 hours for a completion of the reaction. The tubes should be read in daylight as artificial light may cause a false interpretation of the changes.

The results of the Lange test are indicated either in the form of a curve, (see charts in Chap. VIII) or in numerals; thus: 0 means no change, 1 a change to red blue, 2 a change to violet, 3 to blue, 4 to pale blue, and 5 to clear; e.g., 5555500000 means that the first five tubes or the dilutions of 1:10 to 1:160 have been entirely discolored, while the last five tubes have shown no change at all.

Mastic Test

The following technic for the Mastic test is described by Cutting:

A stock mastic solution is made by dissolving 10 gm. of gum mastic in 100 c.c. of absolute alcohol. The solution is filtered. This stock solution keeps indefinitely if well

corked. To 2 c.c. of the stock solution 18 c.c. of absolute alcohol are added, and insufflated rapidly into 80 c.c. of distilled water; this makes an emulsion of mastic which is opalescent when held to the light. This solution can be used immediately or after several days. The reaction seems to be more easily read when a solution is employed which has stood for at least a few hours.

A 1.25 per cent sodium chloride solution is made with distilled water, and to each 99 c.c. of this salt solution is added 1 c.c. of a 0.5 per cent solution of potassium carbonate made up with distilled water.

The test on the cerebrospinal fluid is carried out as follows:

Six small test tubes are placed in a rack. These tubes should have been washed thoroughly in tap water, then in denatured alcohol, to remove any old mastic adhering to the sides of the tubes, rinsed in distilled water and dried, conveniently in the hot oven. To the first tube 1.5 c.c. of the combined salt and potassium carbonate solutions are added, and to the others 1 c.c. each. Then 0.50 c.c. of cerebrospinal fluid is added to the first and after thorough mixing, 1 c.c. is transferred from the first to the second, 1 c.c. from the second to the third, and so on, the last cubic centimeter that remains over from the next to the last tube being thrown out. No cerebrospinal fluid should be put in the control. One c.c. of the mastic solution is now added and stirred thoroughly with a glass rod, care being taken to wash the rod with distilled water before going to the next tube of the series.

The racks are set away, and in from twelve to twenty-four hours the end results are read. If the racks are placed in an incubator at 37.5° C., the precipitation is complete in from six to twelve hours.

Kafka and Jacobstahl found that the results were better if one worked with 12 tubes instead of 5, with dilutions of the fluid up to 1:8000 plus a control tube (tube 13). The

same authors also made another modification of the original. Instead of using a 1.25 per cent NaCl solution they titrated the mastic emulsion with a NaCl solution from 0.1 per cent to 1.5 per cent. By these means they found five grades of turbidity, T_1 , T_2 , T_3 , T_4 , T_5 , and three grades of sediment. They used for the test proper (with cerebrospinal fluid) the NaCl concentration that did not show any turbidity with the mastic and the one giving the first sedimentation. This gave them two curves A and B.

While the first modification, calling for the use of the larger number of tubes makes the test more valuable, the second calling for various strengths of NaCl is considered of little value by many authors.

It is claimed by Emanuel, Kafka and Jacobstahl and Eskuchen that the mastic curve varies with the type of the disease of the central nervous system. There are two main types of curves, the luetic and the meningitic. In the various forms of lues of the central nervous system, the maximum precipitation takes place in the first four tubes and also in the last three tubes, (10, 11, and 12), the precipitation in the latter group being called the negative phase.

In the various forms of meningitis, the maximum precipitation takes place in the last four tubes (dilutions 1000, 2000, 4000, 8000).

In the negative or normal fluid there is a fair degree of turbidity in the first and second tubes and very little in the third, fourth, fifth and sixth tubes.

Benzoin Test

The benzoin colloidal test is too new and as was shown by Warnock, too inconstant in its results to require a description.

Relative Value of Colloidal Reactions

The Lange is beyond doubt the most valuable of the colloidal tests on cerebrospinal fluid. With properly prepared

reagents the reaction can be read easily, although it happens occasionally that two samples of the same fluid will give different readings.

The mastic and benzoin tests do not always give sharp reactions nor do they always give the same result in duplicate specimens; yet, when time permits, one should apply these tests for corroborative evidence.

CYTOLOGIC EXAMINATION

The examination of the cells in the cerebrospinal fluid is of extreme importance diagnostically and should be included in every routine examination of the fluid. There are essentially two methods of counting cells; one is the sedimentation, or French method, and the other is the counting chamber method.

The French Method of Cell Counting

This method, originally described by Ravaut, Sicard and Widal, is as follows: 3 to 4 c.c. of fluid is centrifuged for forty-five minutes. The fluid is then poured off and a few drops of the sediment are drawn up into a pipette of small caliber, and put on a glass slide, making a smear of uniform thickness. The slide is dried in the air, fixed in the flame, and stained with methyl blue or with Wright stain and examined under the microscope with the high power or oil immersion lens. The number in each field is now read. The results of this examination are recorded as follows:

0-3 cells per field—normal
4-6 cells per field—suspicious
7-20 cells per field—abnormal
20-150 cells per field—markedly pathologic

Chamber Method of Cell Counting

Either a special counting chamber, such as the one described by Fuchs-Rosenthal, or the ordinary blood counting

chamber, such as the ones described by Thoma-Zeiss or Turk or Neubauer or the new Thoma-Metz may be used.

The Fuchs-Rosenthal chamber (Fig. 44) is larger than the ordinary leucocyte chamber, being 16 mm. square and 0.2 mm. deep, whereas the Thoma-Zeiss chamber (Fig. 45) is only 1 mm. square and 0.1 mm. deep. In order to count only the white and not the red cells a fluid which destroys the red cells is used in counting cells in the cerebrospinal fluid. A 3 per cent acetic acid solution, used for counting white blood cells may be used for this purpose. It is customary, however, to use a special staining fluid. This fluid consists of methyl violet 0.2 gm., glacial acetic acid 5 c.c. and water to make up 100 c.c.

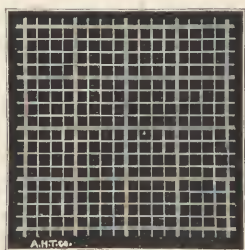


Fig. 44.—Fuchs-Rosenthal chamber for counting cells in cerebrospinal fluid.

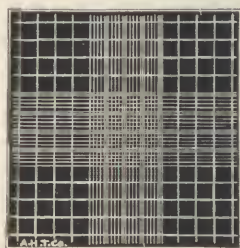


Fig. 45.—Neubauer blood counting chamber which may be used for cerebrospinal fluid.

In the Fuchs-Rosenthal chamber, the cells are counted in the following way: The staining fluid is drawn up into a white cell pipette to mark 1.0 and the cerebrospinal fluid is drawn up to mark 11. The cells in all the 16 squares are now counted. Since the chamber has an area of 16 sq. mm. and a depth of 0.2 mm., the result gives the number of cells contained in 16×0.2 mm. or 3.2 cu. mm. of diluted cerebrospinal fluid. In order to get the number of cells in 1 cu. mm., the number of cells obtained in the field should now be divided by 3.2. However, since the fluid counted was not all cerebrospinal fluid, and since the concentration of the fluid was 10:11 (10 of cerebrospinal fluid to 11 of the

volume) an allowance must be made by multiplying by $\frac{11}{10}$.

In order to get quickly the number of cells contained in 1 c.mm. of undiluted cerebrospinal fluid, the number of cells found in the 16 squares of the chamber should be multiplied by 11 and divided by 32.

In using an ordinary blood counting chamber for counting cells in cerebrospinal fluid, either 3 per cent of acetic acid or the same solution used for staining the cells in the Fuchs-Rosenthal chamber is employed. The staining fluid is drawn up into the pipette to mark 1.0 and the cerebrospinal fluid to mark 11, and the whole ruled surface of the chamber is counted. Since the ruled surface of the blood-counting chamber has an area of 9 sq. mm. and the depth of the chamber is $\frac{1}{10}$ mm., the total count of the ruled surface will be the amount contained in the entire volume which is $\frac{9}{10}$ cu. mm. To obtain the number of cells in one cubic millimeter of diluted fluid, this count should be multiplied by $\frac{10}{9}$. Since to 10 parts of the cerebrospinal fluid, one part of counting fluid was added, this result corresponds to $\frac{10}{11}$ of the number of cells in 1 cu. mm. of pure cerebrospinal fluid. Therefore, in order to obtain the number of cells in 1 cu. mm. of pure cerebrospinal fluid, we have to multiply the latter result by $\frac{11}{10}$.

For quick calculation the number of cells obtained by counting the whole field of the counting chamber (9 sq. mm.) is multiplied by 11 and divided by 9.

Comparative Value of the Two Methods

The centrifuge method of counting the number of cells in the fluid is open to several rather serious objections. First of all the method is not accurate enough as it is not always easy to measure the exact amount of fluid put into the centrifuge tube. Moreover, the size of the drop taken from the sediment of the fluid cannot possibly be

the same at all times. Furthermore, the force of centrifugation and the rate of velocity of the centrifuge are important determining factors. Still another drawback is the fact that the centrifuge method requires a great amount of fluid for counting, more than can usually be spared. For precise results, one should, therefore, use the counting chamber. However, when a rough estimate of the number of cells is all that is required, the centrifuge method is perhaps the more convenient one to use. Another point in its favor is the fact that it enables one to study the type of the cell on one and the same slide.

There is one thing, however, that cannot be emphasized too strongly and that is, that whatever method is employed, the examiner should thoroughly familiarize himself with it and should use it as a standard, so that he can easily detect even a slight increase in the cells. Another thing to remember is that the cells should be counted immediately after withdrawal of the fluid from the body, as they undergo autolysis upon standing.

If for some reason or other the cells cannot be counted immediately, the cells may be preserved by adding 3 drops of dilute acetic acid to each 5 c.c. of cerebrospinal fluid.

When the cerebrospinal fluid is blood stained, the specimen may still be utilized for cell counting, if only a rough count is desired. It is known that under normal conditions the blood contains one lymphocyte to three leucocytes. To obtain the number of lymphocytes, therefore, the white blood cells in the fluid should be counted and the result divided by three.

Type of Cells

In doing a differential cell count, care must be taken to count only the white and not the red cells or the debris. When the fluid is turbid as in meningococcus or in pneumococcus meningitis, a differential cell count may be made directly on the slide without centrifugation. When the

fluid is clear, it is best to centrifuge it from fifteen to thirty minutes through about 1500 revolutions. If the fluid contains only a very small amount of protein, some egg albumin may be rubbed on the slide to prevent the smear from being washed off. Methyl violet, carbol thionin, Wright, Jenner, Leischman and eosin hematoxylin are used by various workers to differentiate the type of cell in the fluid.

A special stain for the cells in cerebrospinal fluid was described by Pappenheim. It consists of 3 parts of a saturated aqueous solution of methyl green and 1 part of a saturated aqueous solution of pyronin. As a rule, however, no special stain is needed for the differential cell count, for methylene blue and next to it the Gram stain show the detailed structure of the cells quite well and stain the organisms at the same time. If tuberculous meningitis is suspected, the special carbol fuchsin stain should be used, as it shows the tubercle bacilli and also stains the cells well.

BACTERIOLOGIC

One must be very careful in doing bacteriologic work on cerebrospinal fluid, for there are many technical factors that may interfere with the success of the work. Such factors may be wrong media, insufficient length of time for the bacteria to develop, contamination of the media, dirty slide, overheating of the slide, (protein particles often look like bacteria) and faulty stains. At times, I have found organisms in a smear done by a novice that did not belong to the cerebrospinal fluid, but were introduced while in the centrifuge tube, or were on the slide which had previously been used for urine examination.

Culture Media

Several drops to 1 c.c. of cerebrospinal fluid are planted on a culture medium. The kind of media to plant the fluid on depends on the type of organism looked for. Most or-

ganisms grow on plain agar. Meningococci have given some workers great difficulty in that they do not grow easily on ordinary media. I have grown meningococci successfully on ascitic dextrose agar and also sheep blood agar. It is strongly advisable to implant every specimen of cerebrospinal fluid on several media, such as blood agar, ascitic dextrose agar, and glucose agar. The culture should be examined microscopically after twenty-four hours' incubation, and also after forty-eight hours, as some organisms do not manifest their characteristics in less than forty-eight hours of incubation.

In addition to the culture media, it is a good plan to put the cerebrospinal fluid left over in the test tube directly into the incubator and to examine it twelve to twenty-four hours later for organisms, as it has been found that some organisms, especially the meningococci, will show up well after the fluid has been incubated for several hours.

Direct Smear

Several cubic centimeters of cerebrospinal fluid are centrifuged for several minutes, the supernatant fluid is poured off and the sediment is put on a slide and stained. Where suppurative organisms are suspected it is best to stain with both methylene blue and gram-stain. When tubercle bacilli are searched for, the fluid should be allowed to centrifuge at high speed for forty-five minutes to one hour and stained by the Ziehl-Neelsen method. It is advisable to examine also the pellicle formed in the tube for tubercle bacilli. If the fluid is very thick, the smear may be taken from the uncentrifuged specimen.

IMMUNOLOGIC

Among the immunologic tests in routine cerebrospinal fluid examinations are agglutination tests for meningococci and pneumococci, precipitin tests of cerebrospinal fluid

with antimeningococcus serum, guinea pig inoculation in tuberculous meningitis, saponin test in cerebral hemorrhage and tumor, and above all, Wassermann test in neurosyphilis. A neutralization test has been described for poliomyelitis.

Agglutination of Meningococci

Two agglutination tests have been described for the meningococcus; the macroscopic and the microscopic.

Macroscopic Method

A polyvalent antimeningococcus serum which has been proved by appropriate tests to agglutinate established



A. B. C. D. E. F.

Fig. 46.—Photograph showing agglutination of meningococci by the macroscopic method.

A. Emulsion of meningococci + 1:10 dilution of antimeningococcus serum.

B. Control of emulsion of meningococci + salt solution.

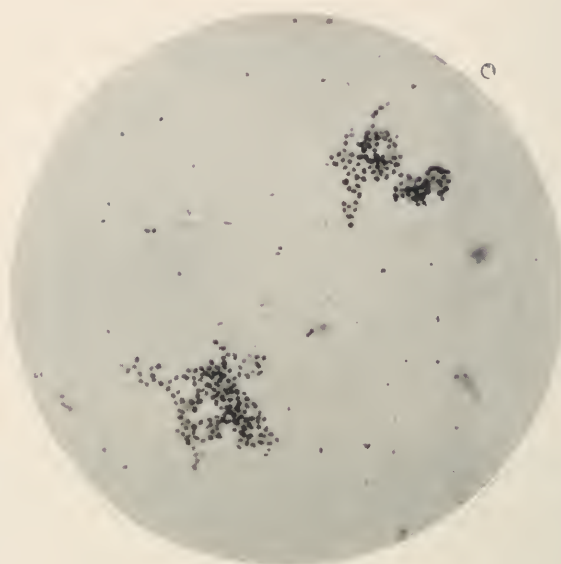
C. Emulsion of meningococci + 1:160 dilution of antimeningococcus serum.

D. Control.

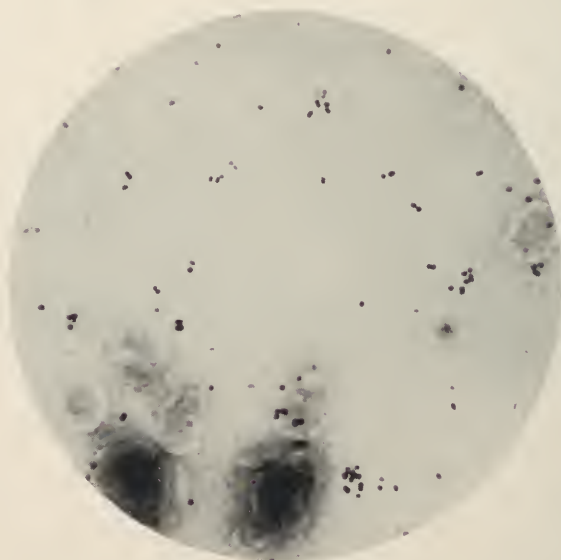
E. Emulsion of meningococci + 1:640 dilution of antimeningococcus serum.

F. Control.

strains of meningococcus in dilutions from 1:200 to 1:2000 is used.



A. Agglutination by specific serum.



B. Absence of agglutination with normal horse serum.

Fig. 47.—Microscopic method of agglutinating meningococci. (Tunicliff.)

A meningococcus culture, preferably only 24 hours old, grown on ascitic dextrose agar or on blood agar is washed down with 2 or 3 c.c. of an 0.8 per cent sterile salt solution; 0.2 c.c. of this meningococcus emulsion is added to a series of small test tubes, each one containing 0.8 c.c. of various serum dilutions such as 1:10, 1:20, 1:40, 1:80, 1:100, 1:500, 1:1000, 1:2000 strength. This is mixed and incubated overnight (15 to 20 hours) at 56° C. Controls of meningococcus emulsion added to 0.8 c.c. of salt solution as well as con-

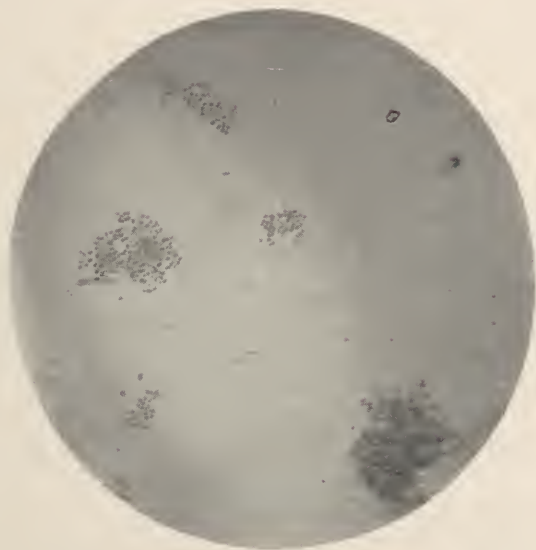


Fig. 48.—Agglutination of meningococci by the microscopic method. (Magnification 800 diameters.)

trols with normal horse serum are also incubated. If the culture in question is meningococcus, a flocculent precipitate will be seen in the tubes containing the bacterial emulsion and antimeningococcus serum, the heaviness of the precipitate depending on the amount of dilution. The controls will be free from precipitate. A true meningococcus is completely agglutinated in 1:200 dilution of polyvalent serum. It is usually also agglutinated in higher dilutions (Fig. 46). The other gram-negative cocci are usu-

ally not agglutinated at all and never in greater dilutions than 1:100. *Micrococcus flavus* sometimes agglutinates in polyvalent and monovalent meningococcus serum in 1:50 dilutions but may be differentiated from the meningococcus by its cultural properties.

Microscopic Method

A more rapid method than the macroscopic for the agglutination of meningococci has been described by Tunnicliff. Equal parts of antimeningococcus serum, whole human blood in sodium citrate solution (one part of blood to 2 per cent sodium citrate in salt solution), and a suspension of organisms are incubated for ten minutes and then stained and examined. Normal horse serum with a suspension of organisms is used as control. In the mixture with normal horse serum there is very little or no clumping of the meningococcus, while in the mixture containing antimeningococcus serum there is decided agglutination (Figs. 47 and 48). The suspension of the organisms is made by adding one or two colonies of the original culture to two or three drops of salt solution. One drop of serum is drawn up in a bent capillary tube, and the upper point marked, then an equal amount of citrated blood and later the suspension of the organisms are drawn up. The content of the pipette is now carefully mixed and heated for ten minutes at 36° C., or left at room temperature for twenty minutes; after incubation the content is blown out on a glass slide, spread with cigarette paper and stained unfixed with carbol thionin or fixed with heat and stained with methylene blue.

Either of the agglutination tests gives good results. I would advise that whenever possible both the macroscopic and microscopic agglutination test should be carried out; when the time is limited the microscopic method can be depended upon.

Agglutination of pneumococci is utilized to determine

the type of the organism, Type I, Type II and Type III, antipneumococcus serum being used for that purpose.

Precipitation of Cerebrospinal Fluid with Antimeningococcus Serum

According to Vincent and Ballot normal cerebrospinal fluid does not form any precipitate with antimeningococcus serum, while fluid from meningococcus meningitis is precipitated, when incubated with antimeningococcus serum.

The technic of the test is as follows: The cerebrospinal fluid is centrifuged till it becomes clear. Two to five drops of antimeningococcus serum are then added to 50 and 100 drops of the clear cerebrospinal fluid. The specimen is incubated at 50° C. for eight to fourteen hours. If the fluid is one of meningococcus meningitis, the mixture becomes turbid. A tube containing cerebrospinal fluid to which no antimeningococcus serum has been added is used as a control.

While other workers have confirmed the observation of Vincent and Ballot, it has been pointed out that at times fluids from other types of meningitis will show the same reaction with antimeningococcus serum. One of the difficulties of the test is that often it is impossible to clarify the cerebrospinal fluid of meningococcus meningitis even after centrifugating it for a long period. This test should therefore be performed only when there is sufficient fluid left over from other more necessary tests.

Guinea Pig Inoculation

It is often necessary to employ the inoculation test to decide whether or not the process is tuberculous in nature.

Five to 10 c.c. of cerebrospinal fluid is injected into the groin of a guinea pig. A month later 0.1 mg. of Old Tuberculin is injected into the axilla of the pig. If the meningitis is tuberculous in nature the pig usually dies the morning

after the injection of the tuberculin. Tubercles are found postmortem in the spleen, the inguinal glands, and various other organs.

It is claimed by some authors that exposure of the guinea pig to x-ray will hasten the appearance of the tuberculous process.

Saponin Reaction

The following technic is used for testing the inhibitory power of cerebrospinal fluid on saponin hemolysis:

Nine c.c. of human blood is drawn from a vein into a flask containing a 1 per cent solution of sodium citrate. The corpuscles are now washed three times and made into a 7 per cent suspension. If human blood is unobtainable, sheep's blood will answer the purpose.

A 5 per cent solution of active saponin in distilled water prepared at intervals of one month or less, is diluted to 1 to 10,000 before the test is performed on cerebrospinal fluid. The amount of saponin necessary to hemolyze the blood corpuscles must be titrated. Hauptmann found 0.4 to 0.7 c.c. as the limit.

Copy

TITRATION		
SAPONIN 1:10,000	SALT	BLOOD
0.4	0.8	0.5
0.45	0.8	0.5
0.5	0.8	0.5
0.55	0.8	0.5
etc to 0.7		

The smallest amount of saponin effecting hemolysis is taken for the test.

After the saponin unit has been determined, 0.8 c.c. of cerebrospinal fluid to be tested is set up with the required amount of saponin and 0.5 c.c. of 7 per cent sheep red corpuscle suspension. Control tubes with normal cerebrospinal

fluid (one known not to produce any inhibitory affect on saponin) and with normal salt solution are also set up. The results are read after 10 minutes in the water-bath at 37° and again after 12 hours in the refrigerator. The setting up of the saponin test with a positive result is illustrated by the following table:

TABLE XLII

				RESULT
Tube 1	1:10,000 Saponin 0.4 c.c.	Normal cerebro- spinal fluid 0.8 c.c.	7% sheep cor- puscle sus- pension, 0.5 c.c.	Complete hemolysis
Tube 2	“	Cerebrospinal fluid to be tested, 0.8 c.c.	“	Inhibition of hemolysis
Tube 3	“	0.85% saline 0.8 c.c.	“	Complete hemolysis

The Wassermann Reaction

It is impossible to describe all the details of the Wassermann reaction in a small volume on cerebrospinal fluid. I shall therefore, limit myself here to only those factors in the Wassermann reaction that have a special bearing on the subject of cerebrospinal fluid.

Different kinds of antigen are used for the Wassermann test, (a) an aqueous extract of syphilitic liver (original method); (b) an alcoholic extract of syphilitic liver; (c) an alcoholic extract of normal liver; (d) an alcoholic extract of heart (either human or beef) reinforced with cholesterolin; (e) ether soluble, acetone insoluble extract of heart.

The complement consists of blood serum of healthy guinea pigs diluted with sterile normal salt solution.

The amboceptor (antisheep antibody) is contained in the serum of rabbits immunized with washed sheep corpuscles.

If the cerebrospinal fluid contains syphilitic antibodies, the antigen combines with the syphilitic antibody and the complement, so that when antisheep amboceptor and sheep cells are added, the complement is already bound and therefore hemolysis cannot take place. If there are no syphilitic antibodies in the fluid, the complement unites with the antisheep antibody or amboceptor and the sheep corpuscles and produces hemolysis. Table XLIII shows the process in the Wassermann reaction of both syphilitic and nonsyphilitic cases.

TABLE XLIII

POSITIVE	NEGATIVE
I. Antigen + Syphilitic Antibody + Complement II. Antibody or Antisheep Amboceptor + Sheep Corpuscles	I. Antigen II. Complement + Antibody or Antisheep Amboceptor + Sheep Corpuscles

The amount of fluid used for the Wassermann test is not always the same. Some use as little as 0.2 c.c. of fluid, whereas others, notably Thomson, use as much as 1.0 and even 1.2 c.c. It has been found that the small amounts do not give positive results as frequently as the larger. This fact, I believe, explains the great number of negative Wassermann reactions on cerebrospinal fluid by the older authors who used very small amounts for the tests. On the other hand, large amounts of cerebrospinal fluid such as Thomson advises are likely to be anticomplementary.

Some workers take 0.2 c.c. of cerebrospinal fluid for each of the tubes set up, varying the amount of antigen added to

TABLE XLIV

	TUBE 1	TUBE 2	TUBE 3	TUBE 4	TUBE 5
	c.c.	c.c.	c.c.	c.c.	c.c.
Cerebrospinal Fluid	0.2	0.4	0.6	0.8	1.0
NaCl Solution	0.8	0.6	0.4	0.2	
Antigen	1.0	1.0	1.0	1.0	1.0
Complement	1.0	1.0	1.0	1.0	1.0
Amboceptor plus corpuscles	2.0	2.0	2.0	2.0	2.0

the tubes. As a control 0.4 c.c. of cerebrospinal fluid without antigen is used. Schottmüller advises the use of different amounts of cerebrospinal fluid in each of the test tubes as is indicated in Table XLIV, a suggestion which is accepted by most workers. This gives a more or less "quantitative result" as to the degree of positiveness of the fluid.

TABLE XLV

EXAMINATION OF CEREBROSPINAL FLUID FOR DIAGNOSTIC PURPOSES

I

*Very Important**Immediate Examination For*

Amount

Color

Foam

Cell Count

Differential Count

Cultures

Direct Smear

Noguchi

Ross-Jones

Sulphosalicylic

Mercuric Chloride

Examination after 24 hours

Presence or absence of pellicle

Measurement of sulphosalicylic and mercuric chloride sediment.

Examination of cultures

Agglutination

Lange

Wassermann

Chlorides

II

Less Important

Total nitrogen

Permanganate index

Sugar

Chlorides

H-ion Concentration

Alkali Reserve

Cataphoresis

Mastic Test

It is best to make the Wassermann test with freshly drawn cerebrospinal fluid. If the test cannot be made immediately after the withdrawal of fluid, it should be put away in the ice box without a preservative. The cerebrospinal fluid is not inactivated. Preliminary titrations must be made on antigen, complement and amboceptor before the test is set up. The proper dose of antigen I believe to be one-fourth of anticomplementary unit and the proper dose of complement and amboceptor to be two units each. Control tubes of the cerebrospinal fluid should be set up with the test.

The cerebrospinal fluid, salt solution, antigen and complement are incubated for one hour at 37.5° C. Then the antishoop amboceptor and the sheep corpuscles are added and the solution is returned to the incubator where it is allowed to remain from 30 minutes to 2 hours. At the expiration of this time, it is taken out and examined. If hemolysis is present the test is negative; if there is an inhibition of hemolysis, the test is positive.

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CHAPTER VIII

CEREBROSPINAL FLUID IN VARIOUS DISEASES

In a consideration of the cerebrospinal fluid changes in various diseases it is important to keep in mind that the changes are not stereotyped in character, but that there is a wide range of variation in the cerebrospinal fluid of one and the same disease, depending on the stage and on the severity of the disease. Yet there are many changes that are constant for a given disease. These, I shall attempt to describe in this chapter.

Uremia

The fluid is often increased both in amount and pressure, especially if there are convulsions. The cells are not increased in number. The globulin may or may not be increased. The serum albumin is usually increased. The chlorides are often increased to 0.8 or 0.85 gm. per 100 c.c. of fluid. The urea nitrogen is greatly increased in amount, reaching as high as 55 mg. per 100 c.c., anything above 50 mg. usually being fatal. According to Lockemann and Füh, lactic acid is present in the fluid in large amounts.

Diabetes Mellitus

The cerebrospinal fluid is usually normal in amount, in pressure, and cell count. The amount and pressure may, however, be increased, especially during diabetic coma. It is chemically negative in all respects but in its sugar content, which is greatly in excess of normal. Foster found the sugar in the fluid of 12 cases of diabetes to vary between 0.5 per cent and 3 per cent. My highest finding was 0.38 per cent. In one case I found the sugar content

in the cerebrospinal fluid to be even higher than that of the blood. Acetone and diacetic acid may also be found in large amounts in the cerebrospinal fluid of patients suffering with diabetes mellitus. These two substances usually indicate a grave prognosis.

Jaundice

The color of the fluid is deep yellow and gives a positive bile test; otherwise, the fluid is negative.

Trichinosis

Van Cott and Lutz, Bloch and others found actively motile trichinæ larvæ in the cerebrospinal fluid of patients suffering from trichinosis. The patients, however, showed no symptoms of meningeal irritation.

Tetanus

The fluid from the cases of tetanus examined by me, was negative in all respects.

Chorea

Dupre and Damus found a distinct lymphocytosis in the cerebrospinal fluid of chorea in a boy of eighteen. Bonneix found a lymphocytosis in two of five cases. Thomas and Tinel found a distinct lymphocytosis in a girl of thirteen, suffering from chorea. They found a similar condition in two of four other patients examined a few months later.

Richardier, Lemaire and Sourdel found a lymphocytosis in twelve out of fourteen cases and hypertension in ten. In three cases, symptoms were somewhat relieved by puncture. A number of French observers found a positive Wassermann in chorea and because of this finding, argued in favor of the specific nature of chorea. Leopold and Bernhard found the cerebrospinal fluid in chorea to be normal

in the chemical and cytologic constituents. In the cases of chorea that came under my observation, the cerebrospinal fluid was normal in all respects, including the Wassermann. The cerebrospinal fluid in Huntington's chorea or hereditary chorea is also normal in all respects. The various experiences cited above incline me to the belief that the examination of cerebrospinal fluid is of no special value in the diagnosis of chorea.

Epilepsy

During an epileptic attack the cerebrospinal fluid is increased both in amount and in pressure. During the intervals between attacks, both the amount and pressure of the fluid may or may not be increased. In epilepsy due to syphilis of the central nervous system, the cells and globulin content are increased; in idiopathic epilepsy, both the cells and the globulin content are normal. The same is true of the Wassermann reaction. According to Donath, choline is present in the cerebrospinal fluid of epileptics.

Amaurotic Family Idiocy

The cerebrospinal fluid is usually increased in amount and pressure, but is negative in every other respect.

Mongolian Idiocy

In Mongolian idiocy the cerebrospinal fluid is usually negative physically, chemically and bacteriologically. Stevenson found the fluid from a large number of cases to give a typical luetic gold chloride curve. Some of the cases examined by me gave positive Wassermann and Lange tests; many of them, however, gave negative tests. I, therefore, do not subscribe to the view that all cases of Mongolian idiocy have a luetic origin. There are some that are luetic by coincidence only.

Alcoholic Psychoses

In alcoholic psychosis the quantity of fluid that can be removed in one sitting is greatly increased, it often being possible to remove as much as 30 to 40 c.c. easily. The pressure is greatly increased in this type of psychosis, running, as a rule, from 150 to 300 mm. of water in height. The fluid is clear and colorless; the protein is not increased, and the cells are usually normal both in number and type, although occasionally I have noticed an increase in the cell count ranging from 26 to 30 cells per cubic millimeter.

A number of authors who have been able to detect the presence of alcohol in the cerebrospinal fluid of alcoholic psychosis, suggest that the test for alcohol be used for diagnostic purposes.

Dementia Precox and Paranoia

Dementia precox gives a normal fluid as a rule. Occasionally the pressure is increased. Paranoia also usually shows no deviation from the normal.

Syphilis

The findings in the cerebrospinal fluid in acquired or congenital lues depend on whether or not the nervous system is involved. If there is no involvement the fluid is negative, including the Wassermann test. If there is involvement, which is quite often the case, there is an increase in the amount and pressure of the fluid, in the content of the protein, and in the number of the cells in the fluid, the cells being principally lymphocytes.

Nonne speaks of four reactions in connection with syphilis of the nervous system: positive Wassermann reaction of the blood, increased globulin, lymphocytosis and positive Wassermann reaction of the cerebrospinal fluid. Nonne's results may be summarized in Table XLVI.

TABLE XLVI

	WASSERMANN TEST IN BLOOD	PHASE I GLOBULIN	LYMPHO- CYTOSIS	WASSERMANN TEST IN CEREBROSPINAL FLUID
General paresis	100% Positive	95-100% Positive	95%	100% positive if large quantities of fluid are used.
Tabes without paresis	60-70% Positive	85-90% Positive	90%	100% positive if large quantities of fluid are used.
Cerebro-spinal lues	80-90% Positive		100%	100% positive if large quantities of fluid are used.

In addition to the reactions enumerated above, the gold chloride test in all forms of syphilis of the central nervous system, gives a positive reaction in the syphilitic zone, the reaction varying with the type of the disease. In cerebrospinal lues the change is in Tubes 1, 2, 3, 4, 5, and 6 (1223320000); (Fig. 49); in tabes the discoloration is inconstant, but is usually in Tubes 2, 3, 4, and 5 and sometimes in 6 (0222110000) (Figs. 50 and 52.) In general paresis, the discoloration is usually in the first six tubes and sometimes also in the seventh and eighth (5555552100). (Figs. 51 and 53.)

The incidence of positive Wassermann reaction in the

TABLE XLVII

	GENERAL PARALYSIS		TABES		CEREBROSPINAL SYPHILIS	
	Num- ber of cases	%	Num- ber of cases	%	Num- ber of cases	%
Marie and Levaditi.....	39	73	9	66.6		
Marie, Levaditi and Yamanouchi...	30	93				
Stertz.....	45	88.8	5	60	8	0
Noguchi and Moore.....	60	73	11	54.5	6	50
Wassermann and Plant.....	41	88				
Morgenroth and Stertz.....	8	100				
Plaut.....	54	90			4	0
Nonne.....	?	90	?	50	16	25
Schutze.....			12	66.6		
Marinesco.....	35	94	15	53		
Smith and Candler.....	64	92.1				
Noguchi, Rosanoff, and Wiseman...	56	87.5				
Total.....	432	90	52	56.2	34	19

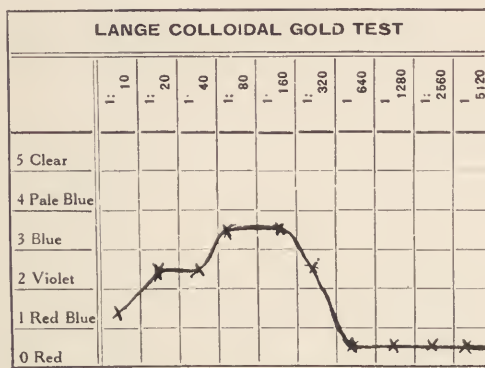


Fig. 49.—Case of cerebrospinal lues.

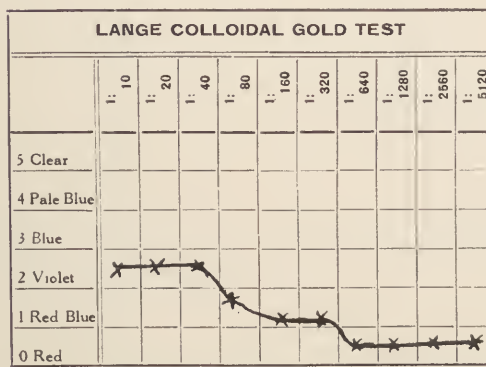


Fig. 50.—Case of tabes.

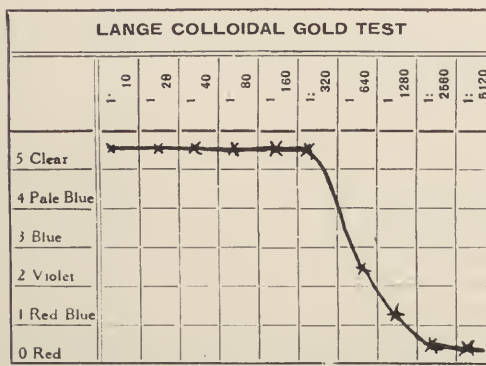


Fig. 51.—Case of general paresis.

cerebrospinal fluid of luetics is seen from Table XLVII of Noguchi.

Hydrocephalus

The amount of fluid which can be withdrawn from the subarachnoid space of the cord depends on the form of the hydrocephalus, whether it is communicative or obstructive. If the foramina of Magendie and Luschka are blocked, very little fluid may be obtained by lumbar puncture. If the communication is open a great deal of fluid may be obtained by lumbar puncture. The pressure also depends on the amount of cerebrospinal fluid in the subarachnoid of the cord, being greatly increased where there is free communication. From the ventricles, on the other hand, a great deal of fluid can be obtained with ease.

The presence or absence of chemical, bacteriological or serological changes depends on the cause of the hydrocephalus. If due to a recent meningitis, the cerebrospinal fluid may show an increase in globulin, an increase in cell count and even the presence of bacteria. If luetic in origin, the Wassermann on the fluid is usually positive. In non-meningitic and nonluetic cases the fluid is negative in all respects except for the increase in amount.

Spina Bifida

The fluid is usually increased in amount in this condition, as is the protein. The color of the fluid is turbid.

Hemorrhage of the Brain

Cerebrospinal fluid removed soon after the hemorrhage occurs is bright red in color due to the admixture of the blood, and contains many red and white blood cells. Fluid from cases of hemorrhage of old standing is yellow (Xanthochromia) and contains only few cells. There are some cases of hemorrhage of the brain in which the fluid is colorless. In cases of recent hemorrhage the fluid is increased in



Fig. 52.—Lunge gold chloride reaction in a case of tabes dorsalis.



Fig. 53.—Lange gold chloride reaction in a case of general paresis.

amount and pressure. In hemorrhages of old standing the amount and pressure of fluid are not increased as a rule. The globulin may or may not be increased. The serum albumin is usually increased due to the blood in the fluid. Cholesterol is present in appreciable amounts.

Skull Fracture

The fluid may be blood-tinged if meningeal hemorrhage occurred; otherwise the fluid is clear. The amount and pressure of the fluid is as a rule unaltered unless a meningitis or an irritation of the meninges followed the fracture; the latter often occurring in connection with depressed fractures.

Sinus Thrombosis

The fluid in the cases of sinus thrombosis observed by me was negative in all respects.

Abscess of the Brain

In the early stages the fluid is usually clear and under slightly increased pressure. The cells range between 9-10 per c.mm. The globulin may be slightly increased. In the terminal stages of brain abscess, a secondary meningitis may develop with corresponding changes in the fluid. At times the secondary meningitis is localized to the part of the brain in which the abscess is located. Occasionally it happens that the abscess breaks through the cortex of the brain and is emptied into the subdural space. In that case the fluid is turbid, the cells are greatly increased and even organisms originally causing the abscess may be present in the cerebrospinal fluid. The following cases illustrate the character of the fluid in brain abscess:

M. G.—Had influenza-pneumonia several months before entering hospital. Fell off 1 story 2 months before. Admitted to hospital in coma with a temperature of 99° F. Recovered consciousness and went into coma again. Kernig, Brudzinsky and Babinsky signs were positive at times. There was also a rightsided paralysis,

The cerebrospinal fluid drawn by lumbar puncture was clear and under marked pressure. It contained nine cells per c.mm., all of which were small lymphocytes. The globulin was slightly positive. Sulphosalicylic acid produced a slight turbidity, mercuric chloride also gave a slight turbidity, but settled in a few minutes in a rather heavy precipitate. After 24 hours the mercuric chloride precipitate remained heavy and the sulphosalicylic precipitate was very small. The chloride reading was 0.85 per cent. The Lange test was negative.

A second lumbar puncture was done 4 days later. The fluid was clear but under less pressure than the first time. The cell count was 10 all of which were lymphocytes. The globulin test was slightly positive. The chloride was 0.85 per cent.

The patient became gradually worse. A decompression operation was performed and a large temporal abscess was found on the right side.

W. D.—Brain abscess. Cerebrospinal fluid was clear and under pressure. Cell count was 25 and consisted of 90 per cent small lymphocytes and 10 per cent large lymphocytes. The globulin was negative. Lange test was also negative.

Tumor of the Brain

In tumors of the brain, the amount of cerebrospinal fluid may or may not be increased, depending on whether or not the foramen of Magendie is blocked and on how much irritation of the meninges is present; the cells are usually slightly increased, ranging between 10 to 15 per c.mm. Most of the cells are small mononuclear in type. Occasionally, however, they are large lymphocytes. The cells may occur in clumps. The globulin as a rule is not increased but may be slightly increased. The Lange test may show changes in the 3rd, 4th and 5th tubes (0044230000). Cholesterol may be present in appreciable amounts. Saponin hemolysis of red blood cells is usually inhibited.

Compression of the Cord

Compression of the spinal cord gives rise to a number of manifestations of the cerebrospinal fluid. In tumors of the cauda equina and conus medullaris the Froin syndrome usually makes its appearance. The syndrome shows the following characteristics: (1) xanthochromia or yellowish discoloration of the cerebrospinal fluid; (2) massive

coagulation of the fluid; (3) an increased number of lymphocytes.

In tumors situated at higher levels of the cord, there is an excess of globulin present, but no increase of the cells. There may or may not be a yellowish discoloration of the fluid. In extramedullary compression of the cord there is usually a yellow discoloration of the fluid and an increase in the globulin, but no increase in the cells. Discoloration of the fluid alone, does not indicate compression of the cord, as this condition may be due to the presence of an old hemorrhage of the brain, or even to a puncture of the plexus of veins surrounding the cord.

Encephalitis

Encephalitis may be divided into two types: nonlethargic and lethargic. The nonlethargic type is encountered in the course of other diseases such as poliomyelitis, meningitis, pertussis or any other acute infectious disease. The cerebrospinal fluid therefore, responds to the condition it accompanies. In poliomyelitis the fluid shows the changes observed in this disease; in meningitis it gives the reactions typical of the organism causing the infection. In encephalitis following acute infectious diseases, such as pertussis and measles, the cerebrospinal fluid is increased in amount and in pressure. The cells are either normal or slightly increased in number. The globulins are not increased, as a rule.

In encephalitis lethargica the cerebrospinal fluid is colorless and shows a slight increase in the globulin content. The cells are usually increased, ranging from 10 to 50 per c.mm. The type of cell is not constant. In some cases it is the small lymphocyte, while in others it is the polymorphonuclear leucocyte. An increase in globulin without a corresponding increase in cells has, in my experience, often been the case in encephalitis lethargica. According to Howel the Lange curve is inconstant.

Meningism

In many infectious diseases, notably pneumonia, grippe, otitis media and also in some cases of intestinal intoxication, there are often symptoms of cerebral irritation, simulating a meningitis, although no bacteria are found in the fluid and no meningeal exudate makes its appearance. To cases of this character, Dupré has given the name of meningism. The fluid in these conditions is generally increased in amount, sometimes even to the same extent as in a severe case of meningitis. The pressure of the fluid is also higher than normal. The color, however, is unchanged. The cells at times are greatly increased. Often, however, they are increased only slightly or not at all. The globulin, as well as the bacteriologic test is usually negative. Only occasionally is there an increase in the globulin and in the cells. Caution, however, must be exercised not to make a premature diagnosis of meningism in all instances of negative findings of the fluid, for it frequently happens that cases of tuberculous meningitis and poliomyelitis in the early stages of the disease, give no other changes in the cerebrospinal fluid but an increase in the amount of the fluid.

Tuberculous Meningitis

The amount of fluid in tuberculous meningitis varies with the stage of the disease, being greater in the initial than in the paralytic stage. The pressure at the onset of the disease is very high, ranging between 300 and 700 mm. water in height. The pressure remains high during the irritative stage but decreases during the stage of coma. The fluid is usually clear and transparent throughout the disease, although occasionally it becomes opalescent; it shows a heavy foam on shaking. On standing from one hour to an entire day a pellicle forms, the pellicle being generally suspended in the center with processes projecting from its sides. There is an increase in the number

of cells which range from 30 to 150 per c.mm., most of them being small lymphocytes, although early in the disease there may be a preponderance of polymorphonuclear leucocytes. The protein in the fluid is also often increased in amount. It may, however, be normal in

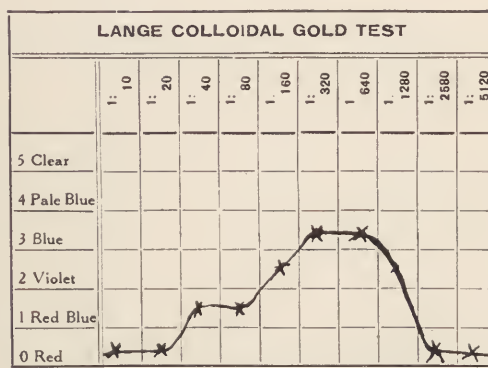


Fig. 54.—Case of tuberculous meningitis.

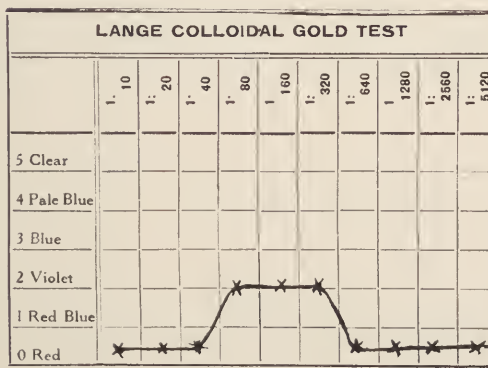


Fig. 55.—Case of tuberculous meningitis.

amount. Albumose and peptone are absent, as a rule, as is also mucin.

The fluid of tuberculous meningitis also shows other variations from normal. The permanganate index is above 2 as compared with the index in nonmeningitic fluid which is below 2. The chlorides are lessened, usually running

below 0.6 gm. per 100 c.c., sometimes falling as low as 0.5 gm. per 100 c.c. The sugar content varies, sometimes equaling the amount in normal fluid and sometimes falling below that of normal. As a rule, however, the sugar content ranges between 0.05 per cent and 0.06 per cent. Phosphates, according to Apelt and Schumm, are present in amounts varying between 0.0034 and 0.0049 per cent.

The physicochemical constants also show a deviation from normal. The average density is given as 1.002, although in my cases, I found it to vary between 1.00626 and 1.00693.

The viscosity varies between 1.0693 and 1.0694. The conductivity is given by Fuchs and Rosenthal as ranging from 0.097 and 0.0225, with an average of 0.0127. The freezing point is usually lowered, running between 0.45 and 0.55.

The H-ion concentration averages a P_H of from 7.4 to 7.6 immediately after the removal of the fluid from the body, with an increase in the alkalinity upon standing, so that one-half hour after withdrawal the P_H of the fluid becomes 7.7 or 7.8. Twenty-four hours after withdrawal the P_H becomes 8.1, 8.2 or even higher. The alkaline reserve runs parallel with the H-ion concentration.

The gold chloride reaction varies, the reaction being 0000233000 or 0000333000. (Figs. 54, 55 and 56.) The ninhydrin test shows a discoloration with the cerebrospinal fluid.

The cataphoresis shows most of the protein moving toward the anode. The sulphosalicylic mercuric chloride ratio is marked, the precipitate with mercuric chloride being three times as great as that of the sulphosalicylic on standing.

Tubercle bacilli are found in the centrifuged fluid only after a careful search (Fig. 57). They are often found more easily in the pellicle. Inoculation of the cerebrospinal fluid of tuberculous meningitis into guinea pigs produces a



Fig. 56.—Lange gold chloride reaction in a case of tuberculous meningitis.

miliary tuberculosis in the animal in course of one to six weeks.

From a diagnostic standpoint the following are the most important changes in the cerebrospinal fluid of tuberculous meningitis: Increase in amount and pressure, increase in the number of cells with a relative lymphocytosis, positive Noguchi, Ross-Jones, and Nonne tests, sulphosalicylic mercuric chloride ratio, high permanganate index, low chlorides, Lange curve, and above all the presence of tu-

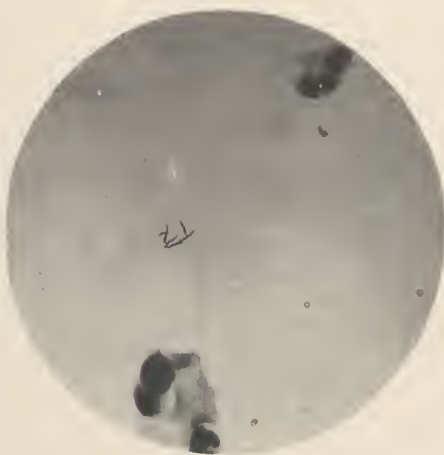


Fig. 57.—Photomicrograph showing tubercle bacilli in cerebrospinal fluid.

bercle bacilli in the fluid, and the development of tubercles in guinea pigs after inoculation.

The following case will illustrate the cerebrospinal fluid findings in tuberculous meningitis:

D. H., eleven and one-half years of age, entered the hospital complaining of headache, vomiting, extreme constipation, anorexia, and weakness. The onset was slow with vomiting and headache, the vomiting being projectile in type. The patient became listless and sleepy. Examination showed marked symptoms of meningeal irritation. A spinal puncture was performed. The fluid obtained was clear and under marked pressure. The cell count showed 320 cells per cubic millimeter, 98 per cent of which were lymphocytes and 2 per cent polymorphonuclear leucocytes. The Noguchi and Ross-Jones globulin tests were strongly positive. The permanganate index was 3.0. The mercuric chloride sediment was four times the size of the sulpho-

salicylic sediment. The direct smear showed no organisms. The blood showed 80 per cent hemoglobin, 5,400 leucocytes per cubic millimeter, of which 58 per cent were neutrophils, 20 per cent small mononuclear and 12 per cent large mononuclear. The Widal reaction was negative, so were the blood cultures.

The child became progressively worse and another spinal puncture was done the next day with practically the same findings as the first specimen with the additional finding of a pellicle when the fluid was allowed to stand. A third puncture showed all globulin tests to be positive, the gold chloride reaction was also characteristic of tuberculous meningitis. The patient died after staying twelve days in the hospital. The postmortem showed a grayish white, purulent exudate at the base of the brain, measuring 0.5 cm. in thickness, the exudate covering the region of the hypophysis and the right optic nerve. A part of it also extended to the right of the longitudinal fissure in the region of the parietal lobe. The exudate showed the presence of tubercle bacilli. Caseated glands were found in the hilus of the lung.

Meningococcus Meningitis

In meningococcus meningitis, the amount of the cerebrospinal fluid is increased, and as a rule, 20 to 40 c.c. can easily be removed by one lumbar puncture. The increase in the amount of the fluid is usually a constant feature of meningococcus meningitis throughout the disease. Only very seldom does it happen that the amount of the fluid is not increased. Cases of this kind usually have an occlusion of the subarachnoid space somewhere along the tract of the cerebrospinal stem. Occasionally the exudate in the spinal canal becomes so thick that no fluid can be obtained by spinal puncture.

The pressure of the fluid in meningococcus meningitis is also increased, ranging between 300 to 700 mm. of water. In two of my cases the pressure was as high as 800 mm. of water.

The color of the fluid varies from a slight opalescence at the onset of the disease to yellowish green later in its course. The yellowish green color is the product of the meningococcus. On standing it sometimes becomes a pronounced green. The fluid remains turbid throughout the course of the disease. It rarely happens that the fluid

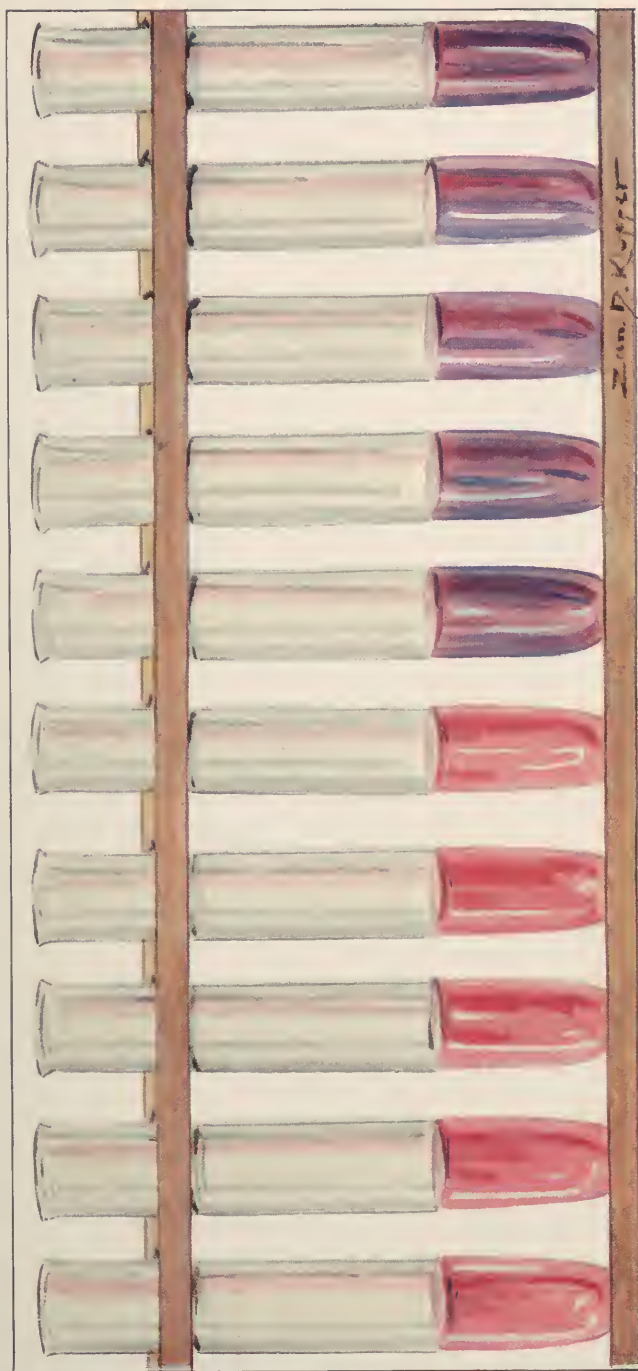


Fig. 58.—Lange gold chloride reaction in a case of meningococcus meningitis.

in the early stages of meningococcus meningitis is clear and colorless. On standing one-half hour or longer the fluid forms a sediment that changes in character with the development of the disease.

(a) In the early stages of the disease, the pellicle is made up of a yellowish-white network, the reticuli being close together forming an opaque layer. The upper portion of the network is balloon- or dome-shaped and the base or lower portion is flattened in appearance. The whole network resembles a small bursa. It usually does not reach the upper level of the fluid and generally it is seen inclining toward one side of the tube.

(b) In the more advanced stages of meningitis, the sediment formation is firmer. It generally spreads out along one side of the tube in the form of a heavy film.

(c) In still more advanced cases, a sediment of yellow granules may be seen attached to one side of the tube. These granules are an indication that the disease has progressed to an advanced stage.

(d) In the very grave cases the sediment is thick and falls by gravity to the bottom.

When the meningitic process recedes, the pellicle or sediment takes on a character the reverse of the one that appeared at its formation.

The chemical changes in meningococcus meningitis are marked. The organic index determined by permanganate is high, ranging between 5 and 7. The protein content is greatly increased, ranging between 0.05 and 7.0 grams per 100 c.c. The Noguchi, Ross-Jones, Nonne and Pandey globulin tests are strongly positive. A 3 per cent sulphosalicylic acid solution gives a heavy sediment on standing measuring from 10 to 20 mm. in height while a 1 per cent mercuric chloride solution gives a sediment much lower than the sulphosalicylic acid. The sugar is usually absent or greatly diminished during the active stage of the disease. Lactic acid may be present in the fluid in large quan-

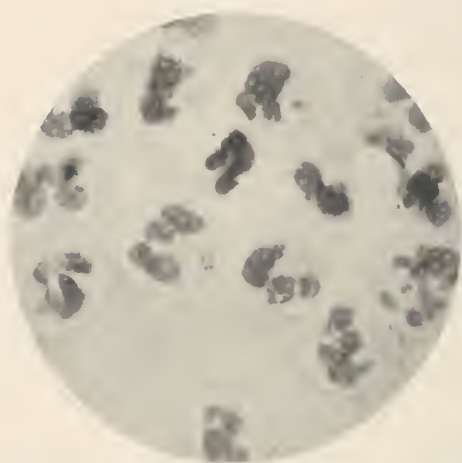


Fig. 59.—Photomicrograph showing direct smear from cerebrospinal fluid of case of meningococcus meningitis.

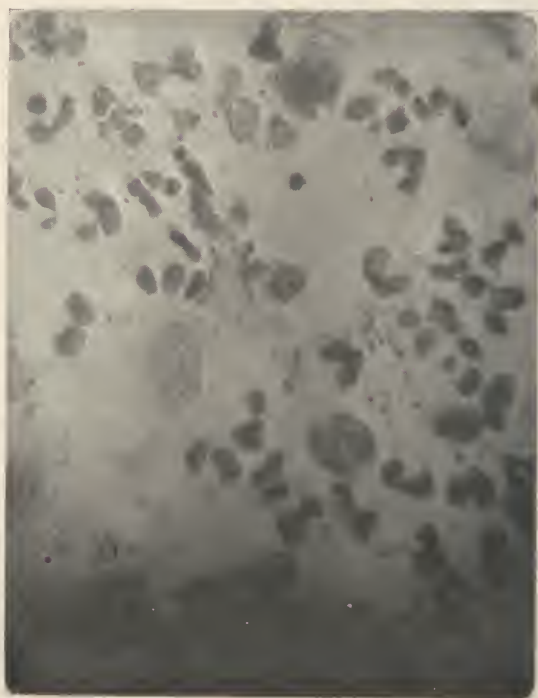


Fig. 60.—Direct smear of cerebrospinal fluid from another case of meningococcus meningitis.

tities. The chlorides are usually the same as in normal fluid, although they may be present in quantities less than normal.

Among the physicochemical changes that take place in meningococcus meningitis the following are important: Cataphoresis shows that the protein migrates to the cathode pole. The H-ion concentration is increased and it continues high for a long time after the removal of the fluid from the body. The alkaline reserve is greatly lowered. The viscosity is 1.0434 to 1.0735. The gold chloride test shows change in Tubes 6, 7, 8, 9, and 10, the reading usually being 0000035555 or 0000005554 (Fig. 58).

The cytologic changes are distinct. The leucocytes are increased in number, varying from 50 to several thousands per cubic millimeter. The greatest percentage of the cells (90 to 98 per cent) is made up of polymorphonuclear leucocytes. The rest of the cells consists of large and small lymphocytes and endothelial cells, the latter being particularly characteristic of meningococcus meningitis. One may also see many unclassified cells in the direct smear. The presence of the unclassified cells and their number vary with the stage of the disease. The greater the destruction of the meninges the greater the number of degenerated cells.

The bacteriologic findings are fairly constant. A gram-negative biscuit-shaped organism is usually found in the direct smear within the leucocytes, some being found also outside the leucocytes (Figs. 59 and 60). The number of organisms found in the direct smear varies. Sometimes there are many organisms all through the field and other times the organisms are few. As a rule, the number of organisms in meningococcus meningitis is not nearly so great as that found in the smears from pneumococcus fluid. It sometimes happens that early in the disease the organisms in the direct smear are very scant in number, but

after the first or second dose of antimeningococcus serum, there is a shower of organisms in the fluid.

On ascitic dextrose agar, the meningococci usually grow in pure culture (Figs. 61 and 62) although it is not always easy to grow them.



Fig. 61.—Twenty-four-hour culture of meningococci grown on ascitic dextrose agar. The culture which has been originally obtained from a case of meningococcus meningitis has been transplanted several times on artificial media, hence the heavy growth in twenty-four hours.

The work of Dopter, Wollstein, Ellis and Gordon showed that there is more than one form of meningococcus in existence. So far two main types and two intermediate types of meningococcus have been recognized. The diagnosis of the

type of meningococcus, however, is a matter of great difficulty.

From pneumococci, the meningococci can be differentiated by the gram stain, the meningococci being gram-negative and the pneumococci gram-positive. It is also possible to differentiate the two by the agglutination test. On the other hand, it is very difficult to differentiate the meningococci from other gram-negative cocci such as gonococcus and micrococcus catarrhalis. However, since these organ-

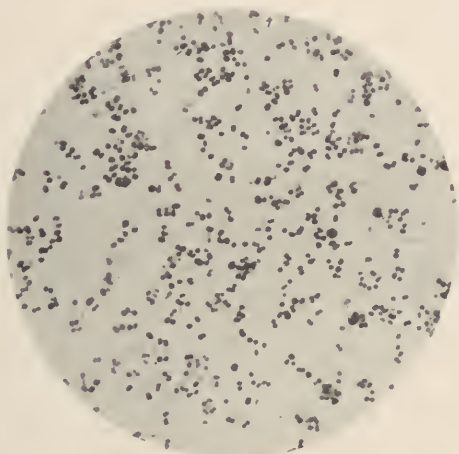


Fig. 62.—Photomicrograph of pure meningococcus culture. Twenty-four-hour growth.

isms rarely ever produce meningitis it is seldom necessary to take them into consideration.

Occasionally it happens that a case of meningitis shows meningococci in the cerebrospinal fluid both in the direct smear and in the culture, but several days later, examination of the fluid shows both meningococci and pneumococci or pneumococci alone. Such cases have been reported by Netter and Salonier, by Mathers and by Fitzgerald. Two such cases of mixed infection also came under my observation.

One must, however, be careful in his staining technic to avoid reaching erroneous conclusions. Above all,

even when the existence of a mixed infection of meningococcus and pneumococcus has been established one must not neglect giving the patient antimeningococcus serum, as this is the only hope left for him.

After several doses of antimeningococcus serum have been administered and the patient begins to show improvement, the cerebrospinal fluid gradually changes in all respects. The fluid becomes less and less turbid by degrees, the color remains yellow because of the color of the serum, but it loses its greenish tint. The amount withdrawn at each sitting is smaller than at the height of the disease; the pressure becomes lower, the protein content becomes less, and the physicochemical changes grow less and less distinct. The cells decrease in number and the type of cell changes from polymorphonuclear to lymphocytic and the bacteria disappear.

The following reports give the average findings in the cerebrospinal fluid of meningococcus meningitis:

I. M. G. Fluid cloudy, cell count 51, differential count 90 per cent polymorphonuclear leucocytes. Noguchi, Ross-Jones, and Nonne, positive. Sulphosalicylic gives heavy precipitate, mercuric chloride produces only turbidity. Sugar 0.01 per cent. No bacteria found in direct smear.

Twenty-four hours later: Gram-negative organism on ascitic dextrose agar agglutinating in 1:200 dilution. Sulphosalicylic sediment measures 20 mm., mercuric chloride 5 mm., protein by modified Esbach 0.1 per cent.

Fluid examined after administration of 30 c.c. of antimeningococcus serum, —very cloudy. Cell count 218; Noguchi, Ross-Jones, and Nonne positive. Sulphosalicylic gives heavy precipitate, mercuric chloride only turbidity. Sugar absent. Gram-negative cocci in smear.

Twenty-four hours later: Gram-negative organisms in culture, agglutinating in 1:200 dilution, sulphosalicylic sediment 24 mm., mercuric chloride 6 mm., protein 0.15 per cent.

Fluid withdrawn after administration of 120 c.c. of antimeningococcus serum is yellow. Cell count 14. Differential count 50 per cent polymorphonuclears. Globulin tests slightly positive. Sugar 0.07 per cent. No organisms in direct smear or in culture.

II. E. C. Fluid turbid. Cell count 14,000; differential count 95 per cent polymorphonuclear; occasional endothelial cell. Noguchi, Ross-Jones, and Nonne positive. Sulphosalicylic very heavy precipitate; mercuric chloride

turbid. Sugar absent. Chlorides 0.6 per cent. Permanganate index 4.0. Gram-negative intracellular diplococci.

Twenty-four hours later: No growth on aseptic dextrose agar. Protein 0.15 per cent. Sulphosalicylic sediment 18 mm.; mercuric chloride 6 mm.

Forty-eight-hour report: Gram-negative diplococci agglutinated by anti-meningococcus serum in 1:250 dilution.

Pneumococcus Meningitis

In pneumococcus meningitis the cerebrospinal fluid is greatly increased in amount, ranging between 20 and 50 c.c. of fluid in one puncture. The color of the fluid varies according to the stage of the disease, but as a rule, it is pearly gray, in contrast to the greenish yellow tinge of the fluid of meningococcus meningitis. On standing, a heavy sediment forms which is usually fibrinous in character, the amount of fibrin being greater in the pneumococcic than in the meningococcic form.

In pneumococcus meningitis, the amount of protein is greatly increased ranging between 0.1 and 7.0 per cent. Thus all globulin tests are strongly positive. The amount of sugar is less than normal and very often is absent altogether. Chlorides are generally present in the same amount as in normal fluid, ranging between 0.6 and 0.74 grams per 100 c.c. of cerebrospinal fluid.

The physicochemical changes are usually the same as in the meningococcus type. The cells in the fluid are numerous, numbering as high as 1000 or more per c.mm. The greatest percentage of the cells are polymorphonuclear leucocytes. The pneumococci which are usually found with ease in the direct smear are present in great numbers. At times there are many gram-positive bacteria in the smear and very few cells. (Fig. 63.)

The bacteria often are arranged in chains of four or six, thus making it difficult to differentiate pneumococcus from streptococcus. However, the fluid of pneumococcus meningitis contains a more fibrinous pellicle than does that of streptococcus. The capsule stain is also of assistance in

differentiating between the two bacteria. The final diagnosis must rest on the character of the culture and on the agglutinative properties of the organism. At times, how-

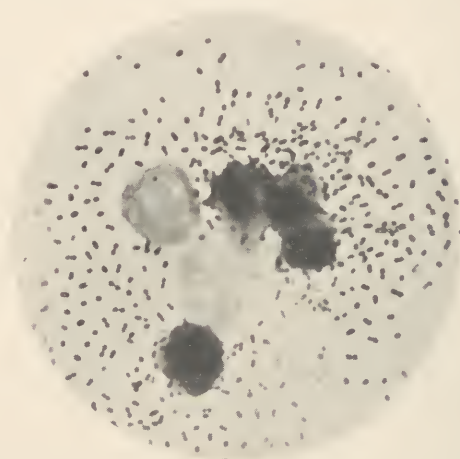


Fig. 63.—Photomicrograph of smear from cerebrospinal fluid of pneumococcus meningitis.



Fig. 64.—Photomicrograph showing smear from fluid of streptococcus meningitis.

ever, there is a mixed pneumococcus and streptococcus infection of the meninges.

E. B., three and one-half months old, brought to hospital with a history of fever and rigidity of neck of one week's duration. Physical examination

showed, in addition to rigidity of neck, a positive Kernig sign, positive Brudzinsky and twitchings of the right side of the body. The cerebrospinal fluid removed by lumbar puncture, was increased in pressure and very turbid. The cells numbered 1400 per cubic millimeter, of which 52 per cent were polymorphonuclear leucocytes, and 48 per cent were lymphocytes. Noguchi, Ross-Jones, and Nonne globulin tests were positive. Sulphosalicylic gave a heavy turbidity and mercuric chloride only a very slight turbidity. The chlorides were 0.66 per cent. Quantitative protein by modified Esbach 0.1 per cent. The gold chloride test gave a complete discoloration in the seventh, eighth, and ninth tubes. The direct smear showed gram-positive, lancolated organisms, arranged in pairs, which, however, did not agglutinate with either Type I, Type II, or Type III antipneumococcus serum.

The patient became progressively worse. Another lumbar puncture was made twelve hours later, but only 2 c.c. of very thick cerebrospinal fluid was obtained. A ventricular puncture was thereupon made and 25 c.c. of cerebrospinal fluid was obtained. The fluid was turbid but not as turbid as that obtained by lumbar puncture. The cells numbered 150 per cubic millimeter, the globulin tests were all positive, the chlorides read 0.74 per cent and the direct smear showed the same organism as in the first fluid.

Twenty c.c. of polyvalent antipneumococcus serum was injected into the ventricle by gravity method. The patient, however, grew constantly worse and died eighteen hours after the injection of the serum.

Streptococcus Meningitis

In my experience, hemolytic streptococci were found to be the most frequent type of streptococcus producing meningitis, although many cases of nonhemolytic streptococcus meningitis have also come to my attention.

The cerebrospinal fluid of all forms of streptococcus meningitis is very turbid. It is increased in amount and in pressure. The protein content is also increased and all globulin tests are positive. The cells are also increased and 90 to 95 per cent of them are polymorphonuclear leucocytes. The streptococci are found in the direct smear (Fig. 64) and in culture. To differentiate between the types of streptococcus, the fluid should be put on blood agar. The hemolytic streptococci will produce hemolysis.

Influenza Meningitis

This not infrequent form of meningitis gives an increased amount of fluid which varies in color from a slight

opalescence to a distinct yellow. The cells in this condition are increased in number and range from a hundred to several thousand per c.mm. As a general rule, the cells are almost entirely polymorphonuclear, although occasionally one may find as high as 40 to 50 per cent of the cells to be lymphocytes. Gram-negative bacilli are found extracellularly in the direct smear in large numbers, the organisms often showing marked pleomorphism (Figs. 65 and 66). A special medium containing hemoglobin is required to grow the influenza bacilli.

According to Rivers, indol can be detected in cerebrospinal fluid from cases of influenza meningitis by adding Ehrlich's reagent (paradimethylamidobenzaldehyd, 4 parts; absolute alcohol, 380 parts; concentrated hydrochloric acid, 80 parts) to an ethereal extract of the cerebrospinal fluid. An old rose color at the point of contact between the two fluids indicates the presence of indol. This test is claimed by the author to be negative in every other form of meningitis.

Colon Meningitis

In colon meningitis the fluid is brownish or yellowish-brown in color. There is an increase in the number of cells in the fluid, most or all of the cells being polymorphonuclear leucocytes. The colon bacillus is found both intra- and extra-cellularly. The culture shows short gram-negative bacilli which acidify and coagulate milk and ferment all forms of sugar.

Typhoid Meningitis

Although uncommon, typhoid meningitis is not rare, over 30 cases having been reported in the literature. The fluid in typhoid meningitis is usually increased in amount and pressure. It is turbid and it contains several thousand cells per cubic millimeter. The type of cells varies with the case. In some cases mononuclear cells predominate; in others

there is a predominance of polymorphonuclear cells. The typhoid bacillus, slightly motile and gram-negative, is usually seen in the direct smear and is easily cultured. The organism agglutinates with antityphoid serum in dilutions as high as 1:3000.

Anthrax Meningitis

The cerebrospinal fluid is always bloody, and contains large numbers of anthrax bacilli.

Rare Forms of Meningitis

Gonococcus and diphtheria meningitis have been reported in the literature. These conditions are very rare, however. Their findings are the same as those manifested in other forms of suppurative meningitis. The diagnosis in these conditions can be made upon recovering the bacteria from the cerebrospinal fluid and culture.

Syphilitic Meningitis

Chronic syphilitic involvement of the meninges is rather frequent, but as a rule remains unrecognized, giving few symptoms or signs. Acute syphilitic meningitis is less frequent, but it does occur occasionally and one must always keep it in mind in cases where a meningitis exists and where the exciting organisms cannot be recovered from the cerebrospinal fluid culture, and where the clinical symptoms do not justify a diagnosis of either tuberculous meningitis or poliomyelitis.

The cerebrospinal fluid in acute syphilitic meningitis is clear or slightly opalescent. It is moderately increased in amount, running generally from 15 to 25 c.c. of cerebrospinal fluid at one sitting. The fluid is moderately increased in pressure. The globulin tests are positive. The cells are greatly increased in number, running between 100 to 600 cells per cubic millimeter; 60 to 80 per cent of the cells are lymphocytes. The smears and cultures are nega-

tive to bacteria, but on careful search with the India-ink method one may find the presence of *Spirocheta pallida*.

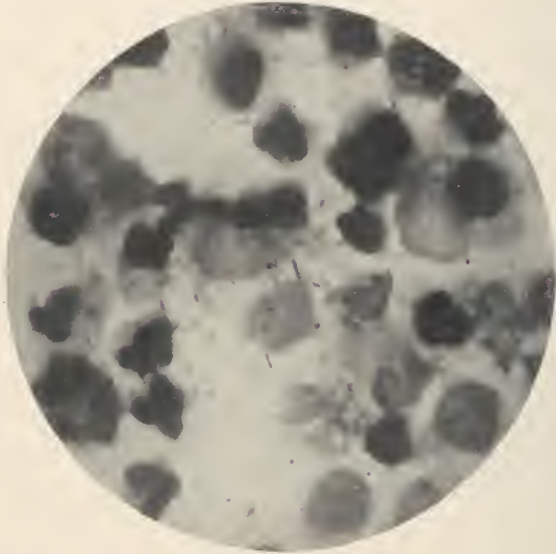


Fig. 65.—Photomicrograph showing direct smear from cerebrospinal fluid of case of influenza meningitis.

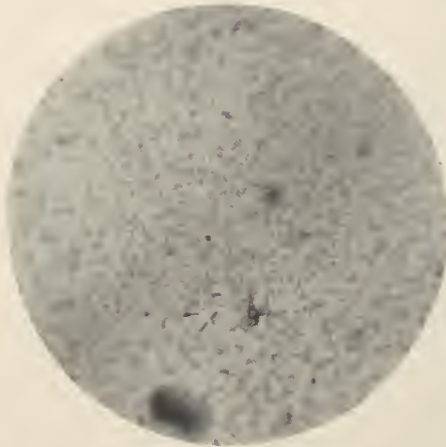


Fig. 66.—Photomicrograph of pure culture of influenza bacilli.

The Wassermann test is positive. The Lange gives a reaction in the syphilitic zone.

Cerebrospinal Fluid in Poliomyelitis

The changes of the fluid in poliomyelitis are most marked in the preparalytic and the first 10 to 15 days of the paralytic stage. After that the fluid may be normal in every respect. The change to be described will therefore refer to the preparalytic and early paralytic stage.

The fluid is increased in amount ranging between 20 to 50 c.c. at one sitting.

The pressure is increased, ranging between 300 to 700 mm. of water in height.

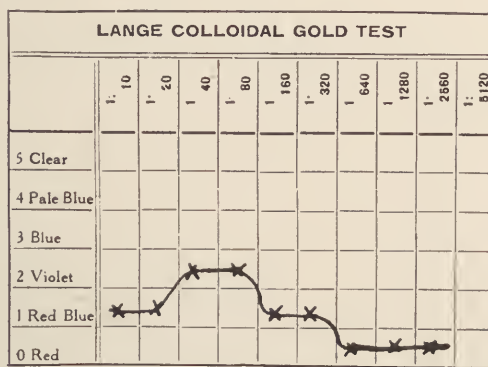


Fig. 67.—Case of epidemic poliomyelitis. First week of disease.

It is usually colorless, only occasionally being opalescent. On shaking the fluid, a thick foam is produced which does not disappear for some time.

The permanganate index is slightly above the normal averaging 1.5 to 2.5. The protein is usually increased in amount, generally giving positive globulin tests, although once in a while the globulin tests are negative.

The gold chloride test in the preparalytic stage, shows either no change at all, or a change in the luetic zone. (Fig. 67.) After the subsidence of the acute symptoms, from the second to the twelfth day, the reaction may be most prominent in the meningitic zone. The cells in this condition are increased in number, 90 per cent of them being of the small, mononuclear type. The increase manifests itself

TABLE XLVIII
CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMAN- GANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSER- MANN	LANGE	SPECIAL TESTS
			(Number of c.c. easily re- moved)			(Number per c. mm., and type)						
Normal	None	Clear	5-10	90 mm. of water in child. 150 mm. in adult	None	1-6 Small lympho- cytes	Less than 2	No	0.05- 0.1%	Negative	Negative	
Uremia	None	Clear	Normal or Increased	Increased	None	Normal	2 or over	-light or marked	Normal	Negative	Negative	Urea may be increased. Chlorides occasion- ally increased.
Diabetes	None	Clear	Normal	Normal	None	Normal	2 or over	No	Above 0.1%	Negative	Negative	Acetone may be present.
Skull frac- ture (without meningeal hemorrhage)	None	Clear	Normal or greatly increased	Normal or Increased	None	Normal	Less than 2	No	Normal	Negative	Negative	
Meningeal hemorrhage (a) bloody	None	Bloody	Increased	Increased	Bloody	Many red and white	Above 2	Yes	Normal	Negative	Negative	Cholesterol present. Serum albumin in large quantities.
(b) clear (Old standing)	None	Clear	Normal or Increased	Increased	None	5-10 small lympho- cytes	2 or over	Slight	Normal	Negative	Negative	Cholesterol present. Serum albumin may be present in large quantities.
Lateral sinus Thrombosis	None	Clear	Normal or Increased	Increased	None	Normal	Normal	No	Normal	Negative	Negative	
Brain tumor	None	Clear	10-15	Slightly increased	None	10-15 Small or large lympho- cytes	Normal	Slight	Normal	Negative	Occa- sionally 0.44230- 0.000	Inhibition of hemol- ysis described by Hauptmann. Increased cholesterol.

TABLE XLVIII—CONTINUED.
CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANENT GANGLION INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGER	SPECIAL TESTS
Brain abscess (a) not ruptured	None	Clear	Slightly increased	Slightly increased	None	10-15 Small lymphocytes Occasionally large lymphocytes	Normal	Slight	Normal	Negative	Occasionally 0.44-0.000	
(b) ruptured	Any organism	Turbid	Increased	Increased	Yes	Several thousand polymorphonuclear leucocytes	Above 2	Marked	Normal	Negative	0.000000-444	
Spinal cord tumor	None	Yellow (Xanthochromia)	Decreased	Decreased	Coagulates spontaneously	None or 1-2	Above 2	Marked	Normal	Negative		
Syphilis of central nervous system (a) Gen. Paresis	None	Clear	10-40	Increased	None; Occasionally small flocculi	40-200 Small lymphocytes	Normal	Marked	Normal	Positive	555550-0000 (Paretic curve)	
(b) Cerebrospinal syphilis	None	Clear	Increased 15-30	Increased	None	100-20 Small lymphocytes	Normal	Yes	Normal	Positive	005555-0000	
(c) Tabes dorsalis	None	Clear	Increased	Increased	None	60-80 Small lymphocytes	Normal	Yes	Normal	Positive	005550-0000 (Tabetic curve)	

TABLE XLVIII—CONTINUED.
CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMAN- GATE INDEX	GLOBULIN INCREASE	SUGAR	WASSER- MANN	LANGE	SPECIAL TESTS
(d) Juvenile paresis	None	Clear	Increased	Increased	None	40-80 Small lymphocytes	Normal	Yes	Normal	Positive	555550-0000	
Meningism	None	Clear	Increased	Increased	None	Normal or slightly increased	Normal	No or slight	Normal	Negative	Negative	
Epidemic encephalitis	Minute filterable virus described by some authors	Clear	10-30	Increased	None	10-20 Small mononuclear	Normal	Slight	Normal	Negative	Negative	
Anterior poliomyelitis	Micrococcus described by some authors	Clear	Increased	Increased	None	10-100 polymorphonuclear very early, mononuclear after second day	Normal	Yes	Normal	Negative	Lutic zone early. Meningitic zone later	
Tuberculous meningitis	Tubercle bacilli	Clear or slightly opalescent	Increased	Increased	Fine & pellicle	30-400 Mononuclear	Above 2	Yes	Normal or less	Negative	Between (1) lutic and meningitic zones. (2) 000023-3000	Cataphoresis to the anode. (2) Sulphosalicylic precipitate 3-6 mm. Bichloride of mercury 6-20 mm. Guinea pig inoculation shows tubercles.

TABLE XLVIII—CONTINUED.
CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMAN- GANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSER- MANN	LANCIE	SPECIAL TESTS
Meningococcus meningitis	Meningococcus	Turbid	Increased	Markedly Increased	Thick, Varying with stage of disease	50-8000; 95% Poly's; Endothelial cells present	Above 3	Marked	Absent or greatly diminished	Negative	Meningitic zone 00000-45555	(1) Cataphoresis to the cathode. (2) Agglutination of bacteria by specific serum. (3) Precipitation of fluid with anti-men. serum (4) Sulphosalicylic acid 7-20 mm., Bichloride 5-6 mm.
Pneumococcus meningitis	Pneumococcus	Turbid	Increased	Increased	Present	50-8000 98% Poly's	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Agglutination. Sulphosalicylic 7-20 mm.; Bichloride 5-6 mm.
Streptococcus meningitis	Streptococcus	Turbid	Increased	Increased	Yes	50-1000 98% Poly's	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Sulphosalicylic 7-20 mm. Bichloride 5-6 mm.
Influenza meningitis	Influenza bacillus	Turbid	Increased	Increased	Yes	50-1000 98% Poly's Occasionally 50% lymphocytes	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Sulphosalicylic 7-20 mm. Bichloride 5-6 mm. Indol test described.
Other Meningitis	Specific organism	Turbid	Increased	Increased	Heavy	50-1000 98% Poly's	Above 2	In-creased	Normal or diminished	Negative	Meningitic zone	

in the preparalytic stage and lasts fourteen to sixteen days after the onset of paralysis. The cells are greatest in number during the first week after the onset of paralysis. The largest percentage of cells (60 to 90 per cent) is of the small lymphocyte type, except in the very early stage of the disease when the predominating cell may be the polymorphonuclear.

The bacteriology of poliomyelitis is still an open question. Flexner and Lewis found a filtrable virus. Mathers, Nuzum and Rosenow report the finding of a micrococcus in the brain and cord. Nuzum reports the presence of the coccus in the cerebrospinal fluid. The organism, according to these authors, is grown best on a 1 per cent glucose broth medium, incubated under aerobic conditions. Other workers dispute the specificity of this microorganism in poliomyelitis. At the present state of our knowledge no positive diagnosis can be made of poliomyelitis by the fluid findings alone. The history of the case and its progress must also be taken into consideration.

The following case might help illustrate the changes taking place in the cerebrospinal fluid of poliomyelitis:

R. E., sick three days with radiating pains in the lower extremities. The cerebrospinal fluid was clear and came out under great pressure. The cell count was 300; 90 per cent of which were lymphocytes and 10 per cent polymorphonuclear. Noguchi positive, Ross-Jones and Nonne negative. Mercuric chloride gave, at the end of 24 hours, double the amount of precipitate of sulphosalicylic acid. The Lange gave a violet discoloration in the first two tubes. The culture was negative. The patient developed a paralysis on the 4th day of the disease.

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CHAPTER IX

INTRASPINAL TREATMENT

Whenever there is a specific remedy for a disease of the central nervous system, it is of the utmost importance that the remedy be brought into direct contact with the central nervous system as early as possible. Even when no specific remedy exists, it may be advisable to introduce some form of medication into the cerebrospinal canal. The injection may be made intraspinally, intraventricularly, or intracisternally.

Intraspinal Treatment of Meningococcus Meningitis

The reports of Flexner and his associates, and the experience of most physicians, have established the fact that the best and most successful way of treating meningococcus meningitis is by means of antimeningococcus serum. The mortality of cases of meningitis that received serum has been reduced to one-half, in some epidemics to one-third, of

TABLE XLIX

EFFECT OF ANTIMENINGOCOCCUS SERUM ON MORTALITY FROM MENINGOCOCCUS MENINGITIS

AUTHOR	CASES TREATED WITH SERUM		CASES TREATED WITHOUT SERUM
	Number	Percentage Mortality	Percentage Mortality
Flexner	1,400	31.4	70-80
Steiner	2,280	37.0	77
Netter	100	28.0	49
Dopter	402	16.44	52.14
Levy	165	18.18	65
Sophian	161	15.5	

the mortality of cases that received no serum, as is shown by Table XLIX from Sophian.

The antimeningococcus serum now in use is prepared by

repeated injections into a horse of dissolved meningococci (culture autolysate meningococci extract), followed by injections of live meningococcus cultures. The cultures used are of various strains of meningococci, so that the serum is polyvalent.

The serum is tested before it is put up in packages, by one of several methods: the complement-fixation method, the agglutination test, the opsonin content and the animal protection test. In England the agglutination test is used very extensively. In France, the complement-fixation method is the one most generally employed. In America, all four methods are used by various manufacturers. McCoy, Wayson and Corbitt of the United States Public Health Service, accept any serum which passes satisfactorily, either by an agglutination or complement-fixation test, as a suitable serum for therapeutic purposes. It has been found advantageous to test the serum to be used with the meningococcus from the particular case in question. Meningococci present so many strains that at times serum will agglutinate several strains of meningococci and still will not agglutinate the particular strain in question.

The antimeningococcus serum is usually preserved with 0.2 per cent to 0.3 per cent of trieresol. The use of this preservative has given rise to a number of objections. Kramer ascribes some of the deaths that had occurred after the injection of antimeningococcus serum to the use of trieresol which he claims has a very depressing effect on the medullary center. It has been found, however, that of the different preservatives used, trieresol exerts the most marked bactericidal effect on the bacteria, and is a much less irritating preservative than chloroform. It is therefore used exclusively in this country as a preservative of antimeningococcus serum.

Whenever a case presents itself that shows signs and symptoms of meningitis, and gram-negative cocci in the smear, no time should be lost in injecting the patient

with antimeningococcus serum. We may even go a step further and say that whenever a turbid cerebrospinal fluid is obtained, antimeningococcus serum should be injected immediately on the probability that the case is one of meningococcus meningitis. Of late the intravenous injection has been advocated, but even when intravenous injection of serum is employed the serum should also be injected into the cerebrospinal canal if there are indications of the presence of meningitis.

The following is the technic of intraspinal injection of serum:

A lumbar puncture is done with the patient lying on his side. (The entire procedure is described in detail in Chapter III.) If the fluid removed is turbid, 15 to 30 c.c. of cerebrospinal fluid is withdrawn, the amount depending upon the pressure of the cerebrospinal fluid. One or two vials, each one usually containing 15 c.c. of antimeningococcus serum which have been kept in the refrigerator, are warmed in warm water to 98 or 99° F. The vial containing the serum is attached to a gravity tube made of rubber with a stylet at the end to fit the lumbar puncture needle (Fig. 68). The stylet of the gravity tube is now introduced into the lumbar puncture needle and the vial is lowered slightly to allow the air bubbles that may be present in the gravity tube to escape and the serum is then allowed to run into the spinal canal. The process of emptying the vial should take from 10 to 15 minutes. If more than 15 c.c. of serum is to be administered, the second vial is attached to the gravity tube after the first vial has been emptied, and the fluid allowed to run in, care now being taken that no air bubbles are allowed to enter the gravity tube during the removal of the vial.

If the serum does not flow readily into the spinal canal the vial containing the serum should be lowered to allow the air bubbles to rise to the surface. If this does not bring the bubbles to the surface, squeezing the gravity tube may do it. This should be done very cautiously, however, to

prevent the pushing of air bubbles into the spinal canal. If the serum still does not flow into the canal, it is advisable to use a small sterile bulb on the vial to press in the fluid. As soon as all the serum has entered the canal the

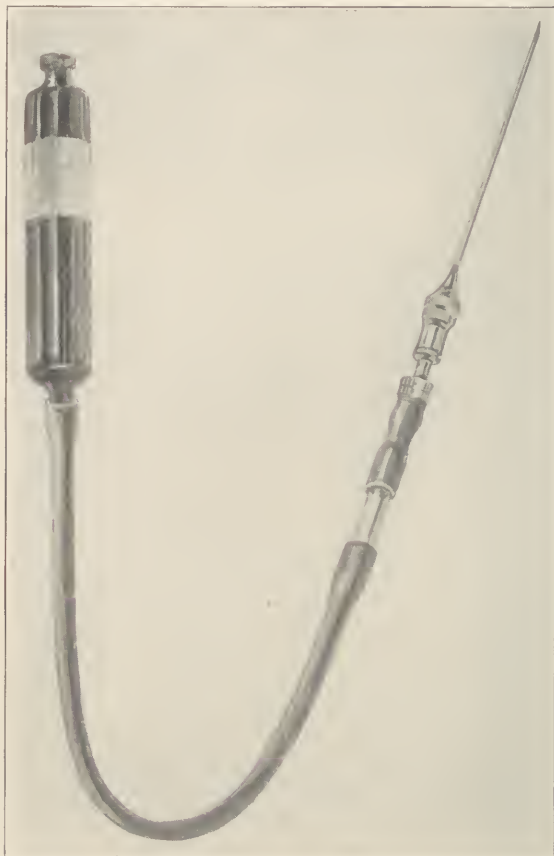


Fig. 68.—Instrument for the introduction of antimeningococcus serum by the gravity method.

needle is withdrawn from the patient's spine and the opening sealed with collodion.

Some authors advise the washing of the spinal canal with sterile salt solution before the injection of serum. In my opinion this procedure is neither necessary nor safe.

As for the dose of serum to be administered at one time, no absolute rule can be given. Sophian advises the use of blood pressure as an index, a marked fall in blood pressure being an indication to stop the injection of serum. One may always guide himself by the amount of fluid removed, inclining toward the larger rather than the smaller dose. For example, it is best to administer 30 c.c. of serum the first time if it is possible to remove 30 c.c. or more of cerebrospinal fluid. If not more than 15 or 20 c.c. of cerebrospinal fluid can be removed at one sitting an attempt should be made to introduce 20 c.c. of serum. If unsuccessful, at least 15 c.c. of serum should be given. I believe that the principle of diphtheria antitoxin, that as much serum as possible be given early, can be applied with the same beneficial effects, to the administration of anti-meningococcus serum.

How often the administration of serum is to be repeated is also a question that has not yet been definitely answered. However, much can be learned from a study of the cerebrospinal fluid and the clinical findings in the particular case. As long as there are bacteria present in the fluid and as long as the cells are numerous and the patient's temperature is high, it is advisable to administer serum twice a day. It has been my plan to administer 30 c.c. of serum the first time, 30 c.c. the second, third and fourth time, at 12 to 18 hour intervals, making 120 c.c. in all, irrespective of the cerebrospinal fluid findings. Then if after a wait of one day the temperature continues high and the cerebrospinal fluid shows the presence of many cells, I administer 30 c.c. more even if no bacteria are present. I then wait two days longer and if the case shows no change for the better I administer 30 c.c. more. The following case illustrates the method I usually follow:

March 24, 1917, 7 P. M. F. A., two and one half years of age, was admitted to hospital with symptoms of meningitis.

March 24, 8 P.M. Spinal puncture done, 45 c.c. of cloudy fluid removed under increased pressure and 30 c.c. of anti-meningococcus serum injected.

Admission No. 96674

Attending Physician

Name J. O.Ward SMH

Intern

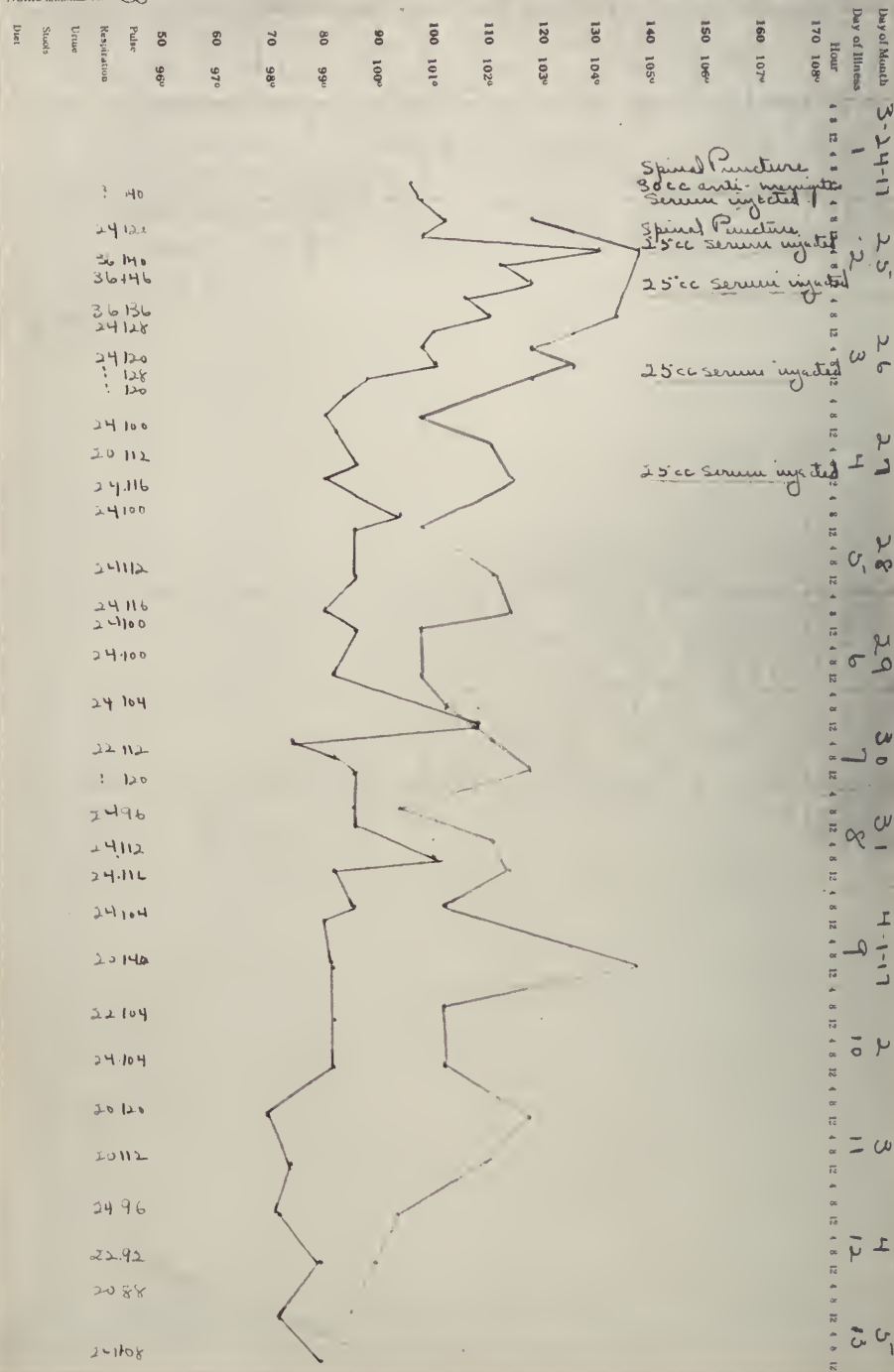


Fig. 69.

Cerebrospinal fluid examination showed 53,280 cells per cubic millimeter, 98 per cent of which were polymorphonuclear. Noguchi, Ross-Jones, and Nonne tests were all positive. Direct smear showed pus cells and gram-negative intracellular diplococci (meningococci).

March 25, 8:30 A. M. Spinal puncture done, 40 c.c. of yellowish cloudy fluid removed under markedly increased pressure; 25 c.c. of serum injected. Examination showed 12,000 cells per cubic millimeter, principally polymorphonuclear. Noguchi, Ross-Jones and Nonne were all positive. Meningococci were found in direct smear.

March 25, 11:30 P. M. Thirty-five c.c. of cloudy, yellowish fluid removed under slightly increased pressure and 25 c.c. of serum injected. Bouillon cultures made March 24 showed meningococci.

March 26. Twenty-five c.c. of cloudy fluid withdrawn and 25 c.c. of serum injected. Few meningococci found in direct smear, no growth appeared on cultures.

March 27. Thirty c.c. of cerebrospinal fluid withdrawn and 25 c.c. of serum injected. Examination showed 85 per cent polymorphonuclear cells, 10 per cent lymphocytes, and 5 per cent mononuclear cell. Globulin tests positive. No growth on cultures.

March 29. Thirty c.c. serum injected. No meningococci found in direct smear and no growth on cultures.

April 2. Cultures made on March 30 and 31, and April 1 and 2 showed no growth.

Fig. 69 shows the temperature and the pulse curve of a case before and after serum injection. Black line indicates temperature, light line indicates pulse.

The following case I believe illustrates the fallacy of administering antimeningococcus serum in too small doses.

D. B., entered the hospital with a history of restlessness, fever, and convulsions. The cerebrospinal fluid removed on entrance to the hospital showed 352 cells per cubic millimeter, all of which were polymorphonuclear. The direct smear showed numerous meningococci. Fifteen c.c. of antimeningococcus serum was administered intraspinally and repeated in 12 hours. A third dose of 15 c.c. of serum was given the next day, making a total of 45 c.c. of serum. Since no organisms could be found in the cerebrospinal fluid withdrawn by the third lumbar puncture and the patient's temperature was down, the physician decided not to administer any more serum. The patient was discharged from the hospital as cured. Two weeks later the patient was readmitted to the hospital with very severe meningeal symptoms. The cerebrospinal fluid was turbid again and showed meningococci. Sufficient serum was administered this time. The child, however, did not improve. The meningitis became more severe and the patient died from the disease. If the patient had received sufficient serum, she would most likely have recovered from the disease and remained well.

If no serum can be injected into the spinal canal the serum should be injected intraventricularly, especially in infants. The procedure consists of the withdrawal of a certain amount of cerebrospinal fluid from the ventricles of the brain (see Chapter III) and of the injection into the ventricles of the brain of the desired amount of serum. If no cerebrospinal fluid can be obtained from either the spinal canal or ventricles, no attempt should be made to inject serum into the spinal canal, but should be injected intravenously. In adults the brachial vein may be used for this purpose. In infants the serum may be injected into the longitudinal sinus. In desperate cases, serum may be injected into the cisterna magna.

Untoward Effects of Serum

There are very few complications that follow the injection of antimeningococcus serum and those that do occasionally present themselves are not severe enough to counterindicate the use of the serum treatment. Among the untoward effects sometimes following the injection may be mentioned:

1. Shock.
2. Aggravation of symptoms—the so-called serum meningitis.
3. Serum rash.

Shock occurs in a small percentage of cases. The symptoms consist of respiratory failure and contraction of the pupils. The skin is usually pale but occasionally there is a flush of the skin and even an edema. Shock can generally be attributed to the too rapid introduction or to the administration of too large an amount of serum. As a matter of prophylaxis it is therefore important that the serum be introduced very slowly and, if possible, in amounts not larger than the amount of cerebrospinal fluid removed. For safety's sake the blood pressure should be watched and the serum discontinued if the fall in pressure is extreme. It

has already been pointed out in the discussion of lumbar puncture that it is dangerous to remove cerebrospinal fluid in the sitting position in a patient suspected to be suffering with meningitis, because of the risk of producing shock and even death. When shock does occur, the administration of serum should be discontinued, and atropine in fairly large doses such as 1/300 in a child, and 1/100 to 1/50 in an adult should be administered hypodermatically. If the atropine does not relieve the symptoms, one c.c. of a 1:1000 solution of adrenalin chloride should be given hypodermatically. The occurrence of shock should not prevent one from introducing serum intraspinally into the same patient several hours later. In such cases, I would, however, advise the administration of a dose of atropine immediately before administering the serum, so as to prevent the repetition of the occurrence of shock.

Aggravation of Symptoms

Cases have been described in which the patient has become more ill after the administration of serum than before. The exacerbation of symptoms, however, is only temporary and should not arouse any anxiety.

Serum Rash

Antimeningococcus serum, like every other foreign protein introduced into the body, occasionally gives rise to a rash that makes its appearance several days after the administration of the serum. The rash may be macular or papular, but it usually occurs in the form of large blotches similar to those produced by any other serum. The eruption, as a rule, occurs on the fifth or sixth day after the administration of the first dose of serum. It usually starts from the point of injection of the serum, and spreads upwards and downwards. It may involve only a portion of the body or the entire body. Nausea, vomiting and temperature accompany the rash, but they are generally of very

short duration. The appearance of the rash often arouses a suspicion of the coexistence of an acute exanthematous disease such as scarlet fever. However, the history of serum injection and the localization of the rash can generally be depended upon to settle the diagnosis.

Intraspinal Treatment of Pneumococcus Meningitis

Of late the use of antipneumococcus serum has become a matter of common practice in the treatment of pneumonia. One would, therefore, be tempted to use pneumococcus serum intraspinally in the treatment of pneumococcus meningitis. Broadbent reports four cases of pneumococcus meningitis that resulted in recovery after administration of antipneumococcus serum. He, however, gave the serum to his patient by mouth. Drought and Kennedy consider intrathecal injection of antipneumococcic serum mixed with a solution of sodium oleate as the most promising method of treatment. So far very few cases have been reported in which intraspinal injection of antipneumococcus serum has been used and of those that have been reported, none seem to have been followed by any marked degree of success.

Pneumococcus vaccine has been used intraspinally in the treatment of pneumococcus meningitis. The results, however, were not striking.

Optochin has been administered by some intraspinally for the treatment of pneumococcus meningitis. I saw one case of pneumococcus meningitis in which intraspinal injections in one-half grain doses of optochin (ethyl cuprin hydrochloride) were made and the patient, a child of twelve, recovered. The case in question, however, had also had an intraspinal injection of antimeningococcus serum previously and this may have been a factor in the recovery, for another case in which optochin was used did not respond favorably. One needs to see more than one case of recovery attributable to the use of optochin before he can

endorse its use. Those who have used horse serum intraspinally do not report any apparent results from its use. In general, then, one cannot make any positive statements about the good effects of intraspinal treatment in pneumococcus meningitis. However, until something better can be found I would advocate repeated lumbar punctures and the injection of serum corresponding to the type of pneumococcus found in the fluid or polyvalent antimeningococcus serum, or even ordinary horse serum if no other is obtainable, into the spinal canal.

Intraspinal Treatment of Streptococcus Meningitis

In view of the hopelessness of most cases of streptococcus meningitis, I believe it is worth while giving polyvalent antistreptococcus serum intraspinally. In this connection the case reported by Weaver, in which recovery took place after combined intramuscular and intraspinal injections of antistreptococcus serum, is quite interesting.

Intraspinal Treatment in Tuberculous Meningitis

Of the numerous remedies advocated and tried for the treatment of tuberculous meningitis, none have been attended with success. Weak solutions of carbolic acid, creosol, iodine and urotropine have been given intraspinally. Tuberculin in various dilutions has also been administered. Recently intraspinal administration of air has been tried by Ramond and Francois. Thus far, neither intraspinal treatment nor any other form of treatment has been of any value in tuberculous meningitis. A few cases have been reported in the literature here and there of tuberculous meningitis resulting in recovery with healed tubercles; however, from the long list of cases that culminated in death, cases reported both in the literature and in hospital records, one is inclined to doubt the diagnosis of "tuberculous meningitis" in cases reported as having recovered.

Influenza Meningitis

Wallstein described a serum for influenza meningitis that is said to be specific. I treated several cases with it without any favorable results.

Poliomyelitis

Rosenow and Nuzum speak very optimistically of the serum treatment of epidemic poliomyelitis. They prepared a serum which they claim is specific against the organism found by them in the brain and cord and also in the cerebrospinal fluid of anterior poliomyelitis. The question of specific serum treatment of poliomyelitis is still a controversial one, so that it is impossible at present to say just what valuation can be placed on the intraspinal treatment of this disease.

Immune serum is recommended by Netter. However, unless it is given early, before complete damage has been done, the serum has no effect whatsoever. Meltzer recommends the intraspinal administration of adrenalin chloride in poliomyelitis. Lewis, who treated 77 cases with adrenalin, reports good results.

Intraspinal Treatment of Syphilis of the Nervous System

It has been the experience of many workers that the best results in the treatment of syphilis of the nervous system are obtained by introducing salvarsan (arsphenamine) or neosalvarsan (neoarsphenamine) into the spinal canal. Salvarsan or neosalvarsan, however, has too irritating an effect upon the meninges. The Swift-Ellis treatment is therefore more efficient. The Swift-Ellis treatment is based on the principle that the blood serum of syphilitics who have been treated with neosalvarsan has a curative effect, and that the best results are obtained when salvarsanized serum is brought into direct contact with the central nervous system. The method is as follows:

Salvarsan or neosalvarsan in the proper dose is injected into the patient intravenously, usually into the arm. One hour later 40 c.c. of blood is withdrawn from the patient by means of a dry syringe and needle and collected into a sterile centrifuge tube. The blood is allowed to coagulate. The following day the serum is centrifuged for one-half hour till all the cells are sedimented. The centrifuge tube must be plugged with sterile cotton or with sterile rubber caps to prevent contamination of the serum. After centrifugation 12 c.c. of serum is carefully pipetted off with a graduated pipette. The serum is diluted with 18 c.c. of normal salt solution, making a total of 40 per cent of serum. This mixture is heated at 56° C. for half an hour. Then a lumbar puncture is performed, 15 to 30 c.c. of cerebrospinal fluid is removed from the patient and 15 to 30 c.c. of the serum-sodium chloride mixture is warmed to body temperature and injected into the spinal canal. As in any other intraspinal treatment the gravity method of injection should be used here also in order to obviate the danger of shock, although some introduce the serum with a Luer syringe without untoward effects. Another precaution to take is to elevate the foot of the bed one hour after the injection. The patient should remain in bed for at least one day after the treatment. The treatment is repeated once a week, till the Wassermann, Lange and globulin tests on the cerebrospinal fluid become negative, which usually takes four to five weeks.

The Swift-Ellis treatment has many critics. Sachs, for instance, claims that marked paresis and tabes are not influenced favorably by this form of treatment. Halliburton believes that "the intraspinal injection of salvarsan has been abandoned." In spite of the various objections raised, the Swift-Ellis treatment has merit and should be used in selected cases of syphilis of the nervous system. I would only emphasize the great care with which it has to be carried out in order not to infect the patient and thereby set up a suppurative meningitis.

Intraspinal Treatment of Tetanus

When tetanus antitoxin is used as a prophylactic measure it is usually injected intramuscularly. However, when the disease is fully developed intraspinal injection is indicated. Tetanus antitoxin when injected into the blood has been found to appear only in traces in the cerebrospinal fluid. When injected directly into the cerebrospinal fluid by the intraspinal method, the serum comes directly into contact with the tetanus toxin and has a preventative if not a curative effect on the tetanus. Although there are other ways of administering tetanus antitoxin, the intraspinal form of administration is one of the most efficient in the treatment of tetanus, particularly if employed in sufficiently large doses.

The method used in administering the serum is the same as that employed for the administration of meningococcus serum, namely, the withdrawal of cerebrospinal fluid and the injection of the serum by the gravity method, in a somewhat smaller amount than that of the fluid withdrawn. The amount injected may range from 15 to 30 c.c. depending upon the quantity of fluid withdrawn. Intraspinal injection of magnesium sulphate in the treatment of tetanus has been advocated by many authors, notably Meltzer.

Intraspinal Treatment of Chorea

Chorea has been treated by various authors by intraspinal injections. Lacuna used intraspinal injections of magnesium sulphate. Heiman saw no beneficial results in a case treated by him with magnesium sulphate. Porter used horse serum. Goodman reported a series of cases which he claimed were benefited by his autoserum treatment, which is administered in the following manner:

The child is put to bed for four days or longer without medication. At the end of this period 45 or 50 c.c. of blood is withdrawn from a vein and rapidly centrifuged. The supernatant blood serum is then pipetted off and kept on ice. A lumbar puncture is made and about 20 c.c. of cere-

brospinal fluid is withdrawn. The blood serum is now heated to body temperature and 15 to 18 c.c. of serum is injected very slowly into the spinal canal. The patient should be made to retain the recumbent position for at least one hour after injection. One injection is usually sufficient. Occasionally, however, it is necessary to give two, three, or even four injections.

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CHAPTER X

SUMMARY

I have endeavored to show the varied character of the cerebrospinal fluid in health and in disease. In the consideration of normal fluid the following facts were emphasized: (1) that the fluid is colorless; (2) that it circulates in the brain ventricles and in the subarachnoid of the brain and cord; (3) that it is impermeable to most chemicals; (4) that it exerts a protective function; (5) that even under normal conditions cerebrospinal fluid is a most complex fluid consisting of from 98.602 to 99.124 parts of water and 0.874 to 1.398 of solids. The protein content of the fluid ranges from 0.013 to 0.0470 per cent; the mineral content, consisting principally of chlorides and carbonates, ranges from 0.850 to 0.950 gm. per 100 c.c. The other elements contained in the fluid, are in the main, the same as those found in blood, although some of the proportions are different.

I have also pointed out the fact that the H-ion concentration of normal cerebrospinal fluid is practically the same as that of the blood (7.4-7.6) and that CO_2 plays an important rôle in governing the reaction of the fluid, running parallel with the H-ion concentration.

In the discussion of pathologic conditions, I pointed out that there are several types of fluid changes, and that the changes are qualitative as well as quantitative and that the former are of as great if not greater significance than the latter. This was demonstrated by means of the cataphoresis tube, of specific precipitation, by cytological and various other methods.

In the discussion of technic I described both the manner of withdrawing cerebrospinal fluid from the body and the method of examining it after withdrawal. Particular at-

tention was given to those methods that are simple and practical enough to be employed by the physician who has no extensive laboratory facilities. I also pointed out their diagnostic significance and their relation to the clinical manifestations of the disease.

In the chapter on intraspinal treatment I described both the methods of treatment definitely established and those still in the experimental stage.

In conclusion, I should like to call attention to the following lines of research which I believe are of fundamental value in clearing up some of the contested problems in medicine.

1. The origin and function of the cerebrospinal fluid.
2. The chemical and physicochemical changes taking place in the fluid in various diseases and the principles underlying these changes; especially the principle of the Lange gold chloride test.
3. The chemical and physicochemical relation between the cerebrospinal fluid and other body fluids, especially blood.
4. The crystallization of the cerebrospinal fluid.

The solution of these problems will open limitless opportunities for research not only in the field of cerebrospinal fluid, but also in that of every other body fluid.

APPENDIX

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